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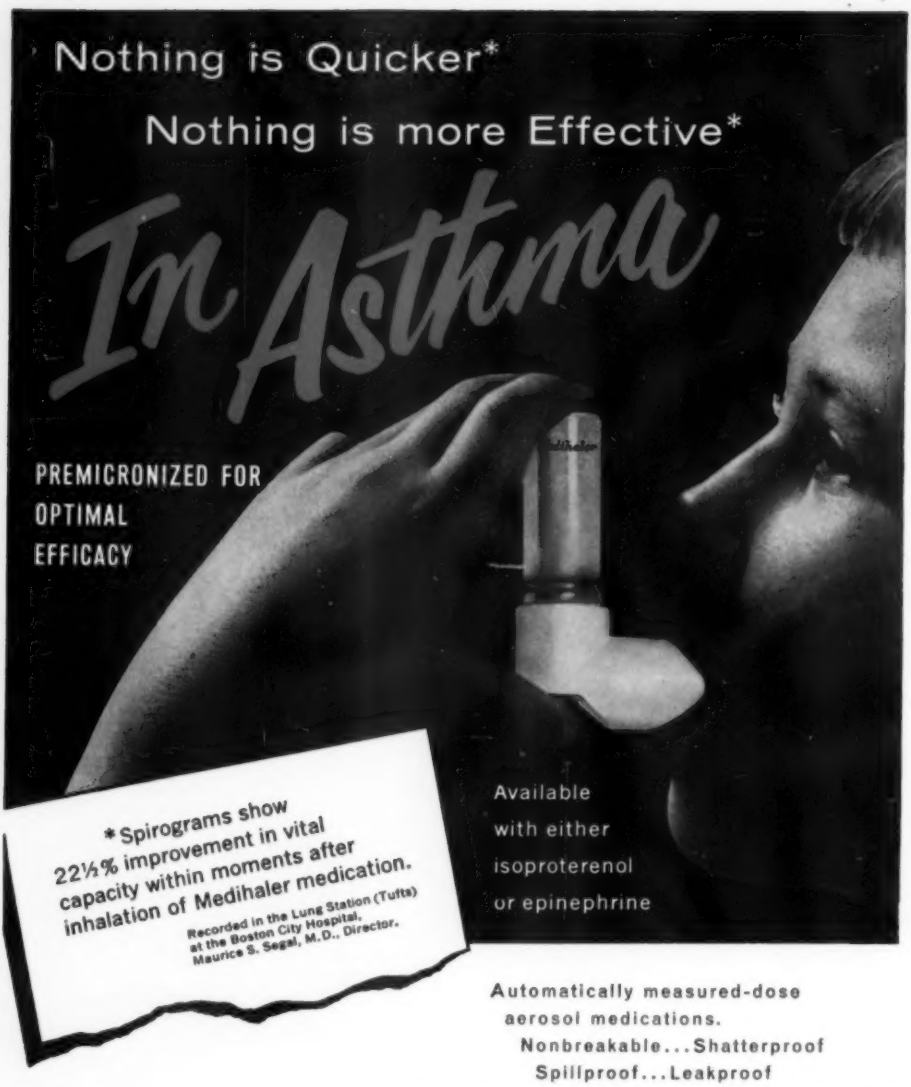
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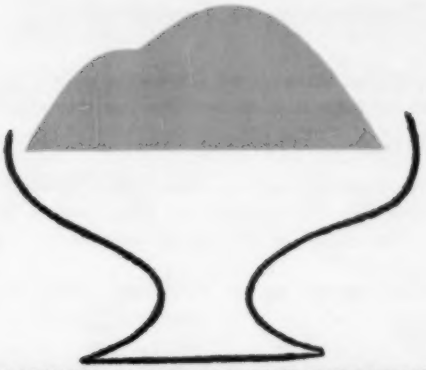

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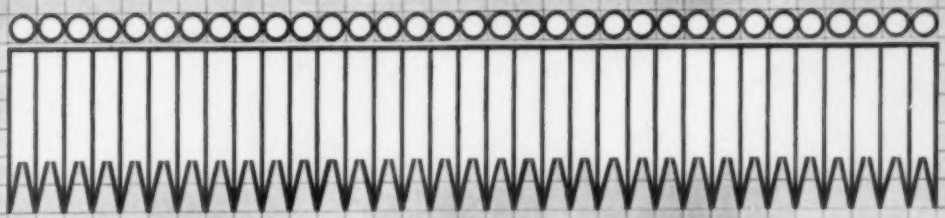

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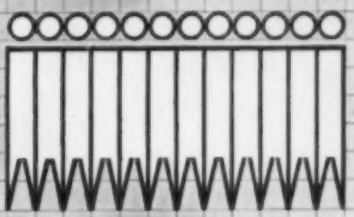

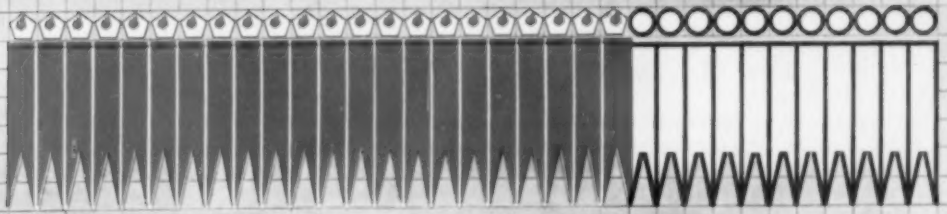

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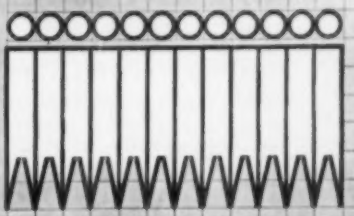

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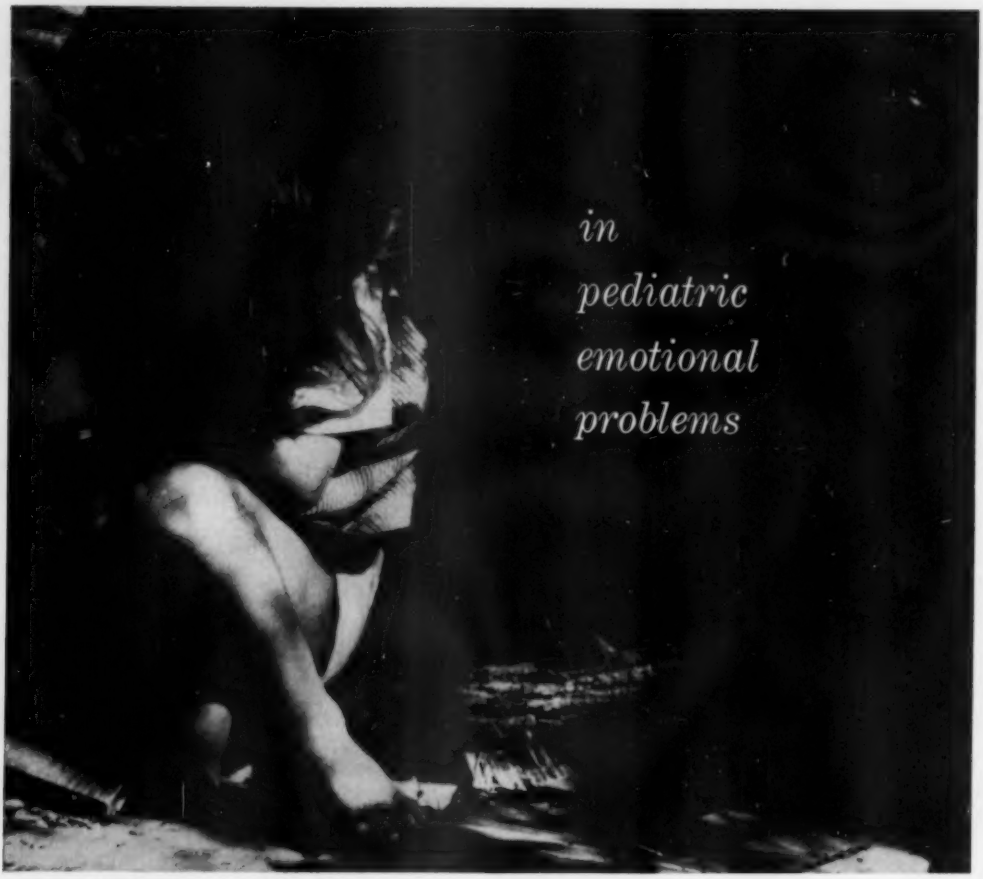

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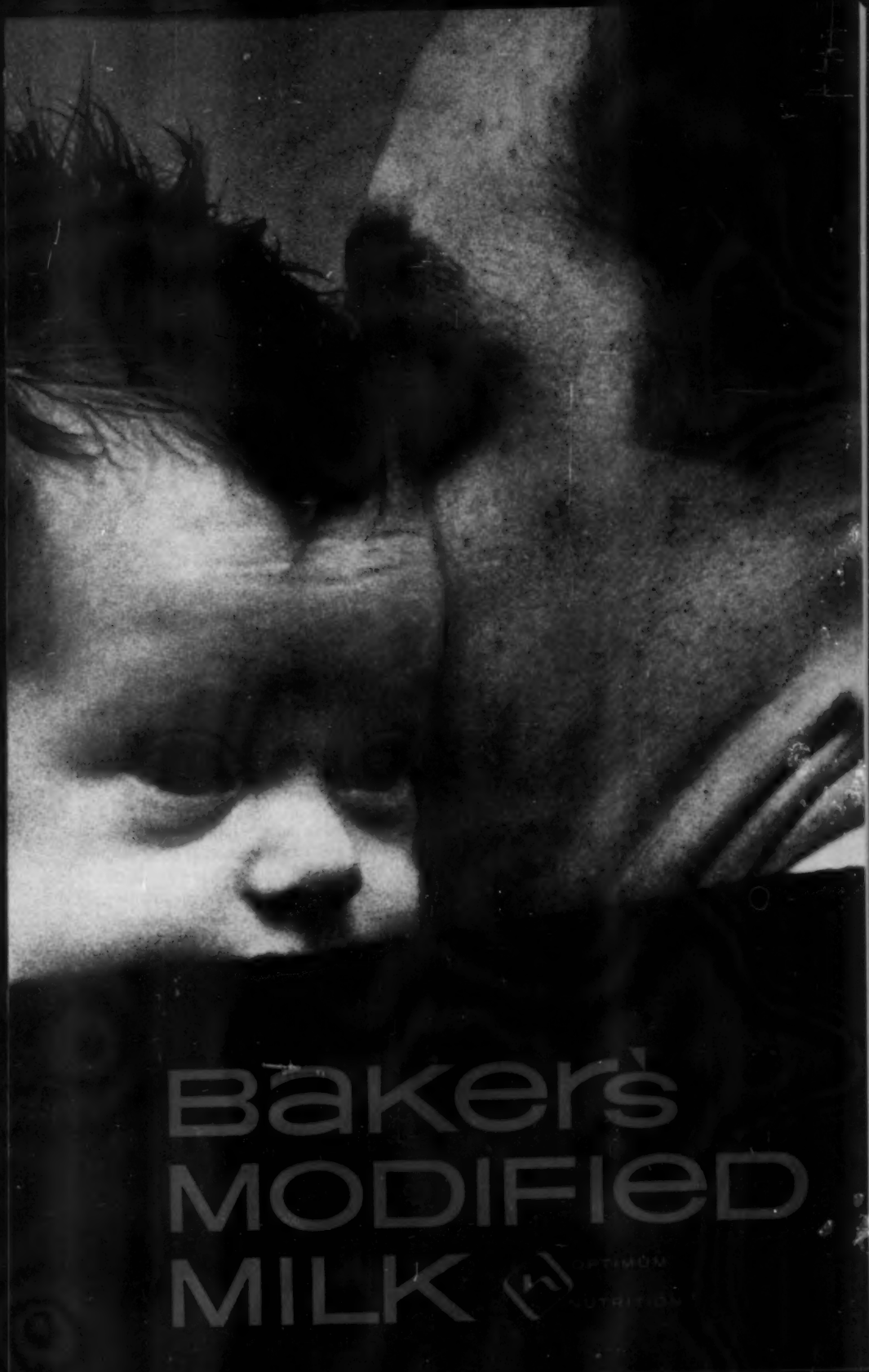
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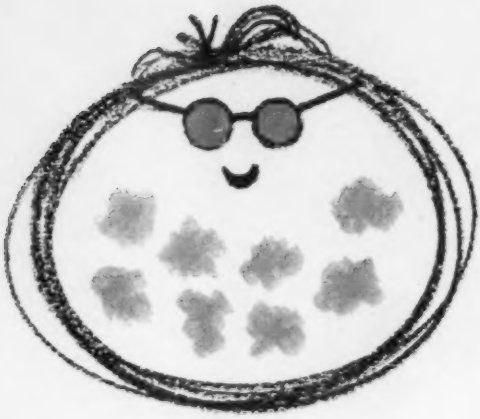

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New Chief Editor Appointed

With this issue, the Chief Editorship of the A.M.A. JOURNAL OF DISEASES OF CHILDREN is officially assumed by Dr. Warren Wheeler. In fairness to Dr. Wheeler, however, it should be pointed out to our readers that, because of the considerable backlog of accepted manuscripts, his influence will not be felt significantly for several more issues.

Dr. Wheeler joined the Editorial Board in 1955. He is Professor of Pediatrics at The College of Medicine of Ohio State University. He graduated from Harvard Medical School in 1933, and received his pediatric training under Dr. Kenneth Blackfan at The Children's Hospital in Boston, becoming Chief Resident there in 1937. Dr. Wheeler's interest in infectious diseases has resulted in many contributions which have influenced pediatric thought, and in fact he holds a simultaneous position of Professor of Bacteriology at Ohio State University. He is a member of the American Pediatric Society, the Society for Pediatric Research, the Central Society for Pediatric Research, and the American Academy of Pediatrics.

Dr. William O. Robertson will be Dr. Wheeler's assistant. Dr. Robertson received his M.D. degree at the University of Rochester in 1949. He interned at Strong Memorial Hospital, and was Assistant Resident and Chief Resident at Grace-New Haven Hospital from 1954 to 1956. From 1956 to 1959, Dr. Robertson edited most of the Ross Research Conference Reports. He is now an Instructor in Pediatrics at Ohio State University, and Medical Director, Central Nervous System Defect Study Center, Children's Hospital, Columbus, Ohio.

It is with regret that I find it necessary, for personal reasons, to relinquish the position of Chief Editor. The two years in that position have been enjoyable. I feel very content, however, that the JOURNAL is in good hands.

RICHARD L. DAY, M.D.

Editorial

Today's Millstone

We may well be disturbed by John Donne's trenchant statement that no man is an island unto himself but is responsible for what goes on in his community. The bell of juvenile delinquency is now tolling for us; nor can we muffle it by contributing to the support of youth study clinics or by shifting our responsibility back to the schools and truant officers, who shift theirs back to the parents. Fundamentally, we are not satisfied with the argument that this is too big, too ramifying a problem for us to tackle, involving, on the one hand, civil liberties—freedom of the press and TV—and on the other, however little we like to admit it, the very structure of our industrial system—progress through automation, the problem of mounting unemployment and mounting costs, and the rights of labor unions. At the bottom of our hearts we know that the bell tolls for the young criminal, arresting him spiritually as well as physically, distorting his mind and soul; at the bottom of our hearts we know his guilt, his distortion, to be our guilt, our distortion.

We need a national day of prayer to meet this crisis, for the present intolerable wastage of spiritual life is caused not by the young people themselves but by social and economic conditions which can be improved if under divine guidance community vision is clarified and a sense of Christian duty awakened.

Let us not deceive ourselves. Our brilliantly expanding industrial society is not at present geared to meet the needs of our youth, and they know it and feel frustrated by that knowledge. There is no place in our industry for these young people. Labor unions have found that they cannot allow a double-wage scale, which by offering cheaper labor would drive out the older workers who, in their forties, are competing none too successfully with vastly increased automation.

Whatever may be the future effect of the interaction of automation and labor unions, one result has already been completed: the industrial disfranchisement of these young people is an accomplished fact. We have created in this country a new and dangerous leisure class, one which is often both ignorant and hostile, with no natural outlets for aggression; even more menacing, a class which continues to have immeasurable influence on younger boys and girls.

No economic or industrial exigency, however great, can justify allowing the rapid growth of this leisure class, many of them mentally ill, many brutalized or under the influence of narcotics, all of them a contaminating nucleus within our society. They present, as did the superior unemployed youth in the days of Germany's Weimar Republic, a potential breeding ground for communism and for the rise of a Hitler to combat it, as well as a breeding ground for race and religious hatred and rioting. The possible violence that can emanate from such a class is terrifying and revolting.

Permission to reprint this article has been obtained from the author and from *Friends Journal*.

Guest editorial, reprinted from the *Friends Journal*, "A Quaker Weekly," of June 27, 1959.
Dr. Miriam Mulford Thrall has taught in various colleges and high schools, and at one time acted as Assistant Principal, in charge of attendance, at a New York City coeducational high school numbering about 10,000.

One of the most tragic ways in which our society has failed the great masses of our children, both delinquent and normal, is our permitting the deterioration in the last 25 years of our formerly unrivaled public educational system. Among the vast horde of teen-agers who are now debarred from being factory hands and are required by law to remain in school, rebellion and frustration have perilously increased, since educators have been unable to provide courses, with conspicuously few exceptions, which will hold their interest. Taxpayers have never been willing to appropriate anything like enough money for the hugely augmented burden that has been placed upon the schools: to provide experienced teachers, rather than substitutes; sufficient classrooms; adequate equipment for up-to-date, advanced work in science or the industrial training needed for apprenticeship in, say, electricity and mechanics.

Good students, too often herded in with the mediocre or below normal, have tended to be disaffected and lazy, with slight incentive to stretch their minds. Those of less ability feel out of place, neglected, either trapped in inadequate industrial courses, or confronted with academic and commercial work beyond their powers or inclinations, or with more general subjects, which seem to them sheer waste of time. Under these circumstances it is not surprising that truancy has increased along with hostility and frustration, for there never has been a sufficient army of officers to enforce regular attendance; that rebellion and delinquency have spread downward through all grades of the public schools in our large cities; and that standards of achievement have steadily declined, since it was early recognized that large percentages of failures would publicize defeat. To close our eyes to these evils or minimize them, as all too many of us today are still doing, is lethal, for they strike at the roots of our nation, and the time is running short in which they can be corrected.

Among the more futile methods that have been suggested to curb juvenile delinquency is the expenditure of vast sums on building and staffing additional prisons and houses of detention. Such places would, however, shortly become so crowded that they would degenerate into concentration camps, with all the injustices and flagrant abuses of law and of human and civil rights for which the camps have without exception been notorious. They would not, moreover, greatly lessen the evil of delinquency since they could not stem its causes. They could at best weed out the more conspicuous young criminals, but would leave the rest of the frustrated and rebellious class to roam our streets and bog down the classrooms of our schools, defeating the efforts of educators to raise standards of instruction.

It would be far better for our government to recognize the needs of these young people than to follow a policy of condemnation and punishment. Implicit in our principle of free enterpise is the right of the worker to work and of the employer to employ. Such rights can be fought for through the ballot; but teenagers, who are the wards of the state and who do not possess the ballot, have been powerless to defend their rights. Nor has their guardian, the state, as yet seen fit to protect them from industrial disfranchisement.

Young people, who are required by a law in whose making they had no share to bear the brunt of war, are now also required by another such law to bear the brunt of economic disorganization. Yet in this latter case they are less qualified than their elders to make the sacrifice, since they are at an age when psychological

and physical drives are at their height, when seething energies demand an outlet, when rebuffs and blockings can do most mental, and therefore most moral, damage.

Leisure, especially for the uneducated and those not culturally prepared to use it wisely, is one of the most dangerous gifts that can be presented. The increasing number of retired businessmen who seek the aid of psychiatrists points to the wisdom of the biblical law, "Six days shall you labor" and of the monastic rule that was later based upon it. Since then vigorous publishers of the doctrine of work, such as the St. Simonians, Carlyle, and Bernard Shaw, have warned against the mental and spiritual depression and warping that almost inevitably accompany idleness.

Yet in spite of the ponderable testimony from the past and the irrefutable evidence amassed by today's psychiatric clinics and mental hospitals, the present trend towards lessened employment, or even no employment, continues—frighteningly continues, for it is far more harmful to deprive people of work today than it would have been at any previous time in our history. The glamours and excitements of television frequently teach not only false values but crime. The headlong pace of our life, the mounting anxieties, the mercurial changes in individual economic, and therefore social, status have too often shattered family well-being and sense of security and have been in part responsible for the rapidly increasing tragedies of both mental disorders and broken homes.

Young people especially absorb the vibrations of tensions around them, quickly losing security and becoming prey to conflicts and aggressions, particularly if a parent tends to be emotionally disturbed. Although mental disease in teen-agers can be comparatively easily arrested if the right treatment and influences are provided, our psychiatric clinics are usually able merely to diagnose and are not fully enough staffed to effect cures, especially since the crowded condition of their present quarters requires that all except a few of their patients must be returned to the same environment which produced the illness. Under these circumstances it becomes inexcusable in our day of scientific enlightenment that the therapy of work is not made available.

It is also inexcusable from a Christian point of view that in the congested areas of our cities, where revolting temptations and dangers are now constant and inescapable, there are practically no opportunities for wholesome outdoor recreation, on which youth is dependent for health and still more for emotional outlet.

Philanthropic clubs such as the YMCA and the Scouts reach only the fringes of our underprivileged sections. In the streets almost no form of physical exercise, except mere walking, can take place without involving some sort of contest which leads, quite naturally since unsupervised, to the development of rival gangs and of gang hierarchy, with its absolute rule and growing terrorism. In the face of this hierarchy, parents, even if conscientious, are often helpless. No punishment which they can decently inflict can compete in severity with that which the gang will mercilessly mete out to resisting or disloyal members. Even if the mother remains at home, she cannot keep young people constantly housed, particularly since the living quarters of the poor are too cramped to admit activity. On the streets there is no way of enforcing obedience, or even knowing of disobedience, until some crime or other infraction of the law has been committed. Furthermore, if children are headed toward narcotic addiction or mental disease, their reactions may become too complicated and threatening for parents to control.

We have reached a crucial point. Society can no longer without grave danger neglect the welfare of children, and the state must intervene to protect its wards. Schools must be returned to their former efficiency, and steps immediately taken to remove frustrated and hostile older pupils and to reduce drastically the size of classes. Space must be requisitioned throughout congested areas for the construction of recreational centers, presumably several stories in height and with grated walls to admit light and air. Factories or work camps must be opened for all physically developed young people who can no longer profitably continue their education. These factories, although under government supervision, should be owned and operated for profit by private enterprise, not by the government but for the production of goods needed by the government, and under government contract. Thus there would be no competition in the open market with unionized factories; nor would the government itself be entering the field of industry.

Such remedial measures would presumably involve far less expenditure of public funds than is now being threatened by the staggering increase of juvenile delinquency, with its accompanying increase of truant and parole officers, police, clinics, and courts, not to mention the projected prisons and detention houses, even one of which would cost more to build, equip, staff, and operate for residence than a dozen recreation centers, which would require only skeleton construction. The centers, it is true, would need to be patrolled by carefully selected policemen, but none of the factories would fall within the city budget; fewer new schools would be required, fewer teachers, and decidedly fewer parole and truant officers, since only cooperative students would remain in the upper grades.

Whatever ultimate balance may be reached, or not reached, among the contending forces of automation, growth of population, and the rights of adult workers to unionize and protect their standard of living, one thing becomes patently clear: the young wards of the state must no longer be the victims of this struggle. It is to be hoped that the wealth of American inventiveness, which has forwarded automation, may now be turned to the creation of new phases of work and new jobs for workers; but it will be small comfort if, when that day arrives, the great masses of our children, the source of our people, have become demoralized.

America is still a vigorous, young nation, with enormous resources and with the genius to utilize them; but to retain this power, we cannot depend solely on the graduates of private schools. The strength of America has hitherto lain in the stamina and sanity of our people as a whole, and the ability of all classes to produce great men, whether statesmen or scientists. If that record is to be sustained, the first and immediate step must be the saving of our children.

Any country that will not protect its youth signs its own death warrant. Such protection must be impartial and carried out by the state itself, not left to philanthropic organizations, which depend largely on voluntary contributions of time and funds, and therefore cannot operate sufficiently widely. The duty of concerned organizations and individuals is rather to proclaim loudly and persistently the obligation of the state to guard and care for its young wards. No governing official or legislative body should be permitted to forget these obligations or to minimize them, for the extent to which a nation allows its children to be harmed measures the weight of the millstone which will drag it down.

MIRIAM MULFORD THRALL, Ph.D.

Studies on Glucuronide Formation in Newborn Infants and Older Children

Measurement of p-Aminophenol Glucuronide Levels in the Serum After an Oral Dose of Acetanilid

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The work of Schmid,[1] Billing, Cole, and Lathe,[2] and Talafant[3] demonstrated that bilirubin has to be conjugated with glucuronic acid before excretion in the bile is possible. It appears that the ability of the liver to form glucuronides is not completely developed in the newborn infant, and this seems to lead to the accumulation of bilirubin in the serum after birth (Vest,[4a] Shirley and Hsia[5]). On the other hand, an increased destruction of red cells immediately after birth, which for a long time was incriminated as a cause of icterus neonatorum, was not borne out by more recent investigations (Findlay, Higgins and Stanier,[6] Fashena,[7] Vest[4b]).

In a previous investigation[8] we demonstrated that acetanilid, a substance of which approximately 80% is excreted in the urine of adults in a conjugated form, appears only slowly in the urine of the newborn and within 24 hours on the average only 10%-25% is excreted. This seems to indicate that the capacity to synthesize glucuronides is only partially developed. It was also shown that this capacity develops rather rapidly and the percentage of conjugated N-acetyl-*p*-aminophenol excreted increases markedly within the first six weeks after birth.

In the present investigation we gave newborn infants and older children acetanilid orally and observed the amount of N-acetyl-*p*-aminophenol, in free form and the glucuronide, in the blood so as to gain an insight into the differences between the glucuronide-conjugating capacity of the liver in newborn infants and older children.

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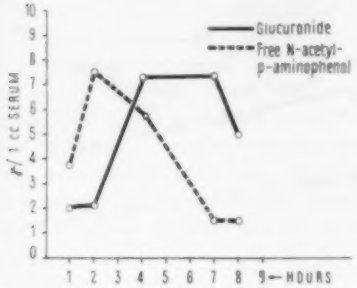
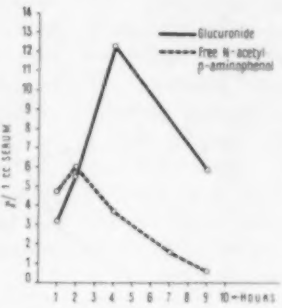
From the Children's Hospital, University of Basel.

Methods

Fifteen children between 6 and 16 years of age, ten newborns, and two infants 25 days and 4 months old were investigated. To the patients in this study 20 mg. of acetanilid per kilogram of body weight was given orally. Blood was taken for the determination of N-acetyl-*p*-aminophenol, free and total conjugated form, whenever possible at 1, 2, 4, 7-8, 9-12, and 24-36 hours after the oral administration of acetanilid. The determinations were made by the method described by Brodie and Axelrod.[9] These investigators showed that acetanilid is first oxidized to N-acetyl-*p*-aminophenol, which is then conjugated at the hydroxyl group. On the average 80% is excreted as a glucuronic or sulfuric acid conjugate in the urine.

In the present study N-acetyl-*p*-aminophenol and the total conjugated *p*-aminophenol (consisting of N-acetyl-*p*-aminophenol and hydroxy-conjugated N-acetyl-*p*-aminophenol) were separately estimated in the serum. This is possible because of the different solubilities of these compounds in ether. The amount of hydroxy-conjugated N-acetyl-*p*-aminophenol is calculated by subtracting the free N-acetyl-*p*-aminophenol from the total conjugated *p*-aminophenol. This method of course does not differentiate the glucuronides from other possible hydroxy conjugates. In many cases we therefore used a second procedure to make sure that we were dealing with the glucuronide. This was done by measuring the amount of N-acetyl-*p*-aminophenol liberated from the serum by the action of bacterial β-glucuronidase (Axelrod, Schmid, and Hammaker[10]). This enzyme specifically hydrolyzes glucuronides. Estimation of the free N-acetyl-*p*-aminophenol before and after enzymatic hydrolysis makes it possible to calculate the amount of N-acetyl-*p*-aminophenol glucuronide.





Figs. 1 and 2.—The course of free N-acetyl-*p*-aminophenol and the corresponding glucuronide in the serum of two children, age 10 and 8½ years.

The hydrolysis was carried out by adding 10 mg. of bacterial β-glucuronidase* to 1 cc. of serum and incubating for 18 hours at 37 C in 4 cc. of 0.15 M acetate buffer, pH 6.2.

It was found that the amounts of hydroxy-conjugated N-acetyl-*p*-aminophenol estimated by the two different methods were equal in most cases. In a few cases the N-acetyl-*p*-aminophenol glucuronide accounted for only 80%-90% of the amount calculated from acid hydrolysis. This indicates that generally most of the hydroxy-conjugated N-acetyl-*p*-aminophenol is present in the serum conjugated with glucuronic acid.

Bilirubin in the serum was determined by the method of Jendrassik and Gróf.[11] The methemoglobin was measured by the procedure described by Evelyn and Malloy.[12]

Results

Figures 1 and 2 are examples of the change in the concentration of free N-acetyl-*p*-aminophenol and N-acetyl-*p*-aminophenol glucuronide in the blood of two of the older children after an oral dose of acetanilid. One sees that the substance is quickly absorbed and oxidized to N-acetyl-*p*-aminophenol. The maximum blood concentration of free N-acetyl-*p*-aminophenol is reached two hours after the oral admin also present at this same time. Thereafter a steep decline in the concentration of free N-acetyl-*p*-aminophenol sets in, while the concentration of glucuronide form continues to climb. The maximum glucuronide concentration is reached approximately four hours after the administration of the acetanilid. The blood concentration declines rapidly after the maximum is reached, and by the seventh to ninth hour there is only a relatively small amount of the glucuronide still present in the blood.

The concentration curve of a 25-day-old infant definitely differs from that of the older children described above (Fig. 3). The formation of free N-acetyl-*p*-aminophenol does not show any significant difference from that of the older children, and the maximum concentration of the free form is reached after two hours, as was also the case in the two older patients. The glucuronide formation in the 25-day-old infant is deficient in that four hours after the administration of the acetanilid only one-half of the maximum blood concentration of glucuronide is reached. The glucuronide concentration curve reaches its maximum only after seven hours but then declines fairly rapidly (Fig. 3).

The tendency for delayed conjugation of the free N-acetyl-*p*-aminophenol with the

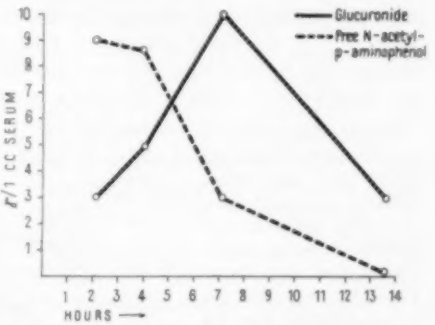


Fig. 3.—The course of free N-acetyl-*p*-aminophenol and the corresponding glucuronide in an infant of 25 days. Weight on the day of examination 3,750 gm.

* Sigma Chemical Co.

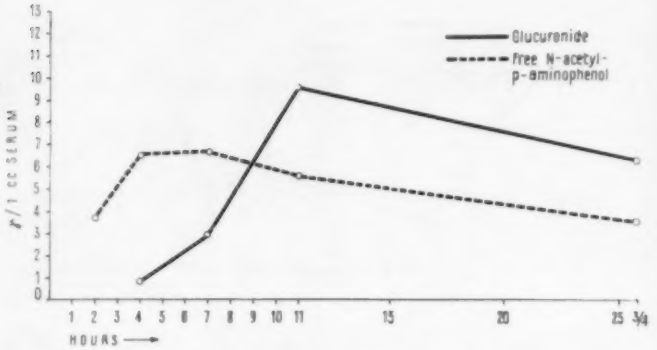


Fig. 4.—The course of free N-acetyl-*p*-aminophenol and the corresponding glucuronide in an infant one day old, weight 3,900 gm. The serum bilirubin concentration was 1.9 mg. %.

glucuronic acid is particularly evident in the newborn. Examples of this are shown in Figures 4, 5, and 6, The one-day-old infant of Figure 4 oxidizes the acetanilid to N-acetyl-*p*-aminophenol fairly rapidly, but a certain delay compared with older children is evident. The maximum blood concentration is reached after four hours but then shows little change up to the seventh hour. After four hours glucuronide appears for the first time in measurable quantities. The concentration of N-acetyl-*p*-aminophenol-glucuronide climbs gradually and reaches a maximum after 11 hours. Twenty-five hours after the administration of acetanilid the concentration of free N-acetyl-*p*-aminophenol as well as the glucuronide form is still relatively high.

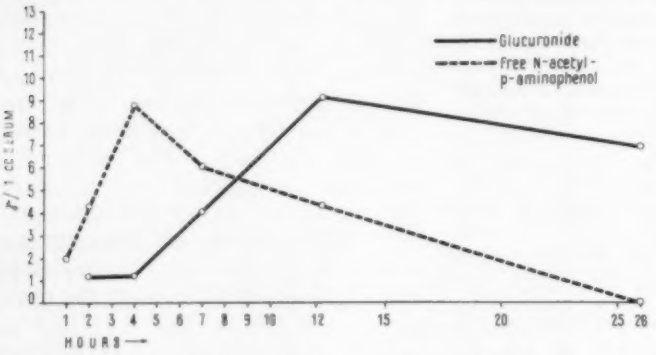


Fig. 5.—The course of free N-acetyl-*p*-aminophenol and the corresponding glucuronide in a 3-day-old infant, weight 4,600 gm. The serum bilirubin concentration on the day of examination was 16.8 mg. %.

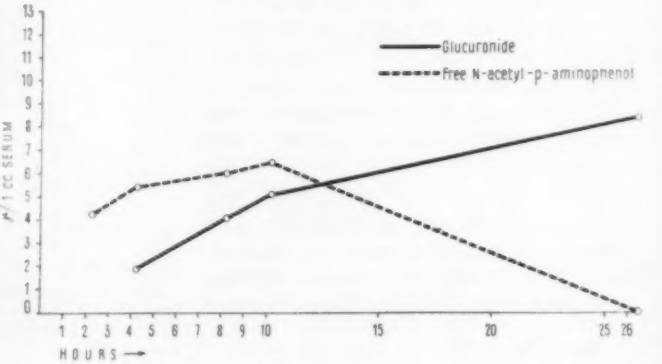


Fig. 6.—The course of free N-acetyl-*p*-aminophenol and the corresponding glucuronide in a premature infant 6 days after birth. On the day of examination the weight was 2,100 gm. and the serum bilirubin was 7.1 mg. %.

A similar picture is presented by a 3-day-old, very large infant (Fig. 5). The fall in concentration of free N-acetyl-*p*-aminophenol in this case is somewhat faster, and after 26 hours the blood concentration was not measurable. At this same time the glucuronide concentration has dropped only slightly below the maximum it reached at the 12th hour. On the day of the test the bilirubin concentration in the plasma of this infant was 16.8 mg. %.

In the case of a 6-day-old premature infant, body weight 2,100 gm. (Figure 6), the rise in blood concentration of the free form and the glucuronide is slower than in any of the cases previously mentioned. The highest glucuronide blood concentration is reached after 26½ hours. At that time we were no longer able to detect free N-acetyl-*p*-aminophenol in the serum.

Comment

In older children the conversion of a given amount of acetanilid into free N-acetyl-*p*-aminophenol and the further conjugation with glucuronic acid occurs at a speed and to an extent which compares closely with the results found in adults by Brodie and Axelrod.[13] The results from the same tests in infants show a considerable difference from those of older children. The greatest difference is found to be in the conversion of the free N-acetyl-*p*-aminophenol into the corresponding glucuronide. This conjugation with the glucuronic acid is much delayed in infants. This is shown in the considerable delay between the administration of the acetanilid and the first appearance of the glucuronide and by the slow increase in the glucuronide blood concentration. Likewise the maximal glucuronide concentration is reached after 11 or more hours instead of 4 hours as in older children. Since the blood concentration of free N-acetyl-*p*-aminophenol declines very slowly after it reaches its maximum, the conversion to the glucuronide apparently progresses at a much slower rate. From this one can assume that the glucuronic acid transferase in the liver of the infant is not yet completely developed. The oxidation of acetanilid to the corresponding *p*-aminophenol appears also to be a little delayed in the infants because the peak concentration is reached later than in children. It is not completely clear if the kidneys play a role in the delayed excretion of the N-acetyl-*p*-aminophenol glucuronide in the newborn infant. In any case, if the excretion of the *p*-aminophenol is comparable with the PAH clearance for infants, the small doses of acetanilid administered can hardly overtax the ability of the kidneys to excrete it. The fact that the infant of 25 days (Fig. 3) is able to excrete the glucuronide rapidly, even though the tubular secretion in the kidney does not reach its complete development before the first year, (Smith [14]) speaks for this assumption. This leads us to believe that the development of the tubular secretion does not have much bearing on the glucuronide excretion. Furthermore, our studies on the excretion of N-acetyl-*p*-aminophenol in the urine of infants show that the development of the glucuronide-conjugating capacity of the liver after birth (Vest [8]) is much more rapid than that given by Smith [14] for the tubular secretion of the kidney.

The question arises as to how much connection there is between N-acetyl-*p*-aminophenol glucuronide formation and the formation of bilirubin glucuronide. The enzyme system which consists of glucuronic acid transferase and uridine diphosphate glucuronic acid (UDPGA) is responsible for the conjugation of the glucuronic acid with the *p*-aminophenol, and, according to the work done by Schmid, Hammaker, and Axelrod,[15] and Grodsky and Carbone,[16] is also necessary for the formation of bilirubin glucuronide. It therefore seems justified to assume that in the newborn infant not only the formation of the aminophenol glucuronide but also that of bilirubin glucuronide is delayed. This delay leads to an

accumulation of bilirubin in the plasma. Icterus neonatorum can then be said to be due to an insufficiency of the glucuronic acid transferase system in the liver of the newborn.

There is a definite correlation between the infants in our investigation and the newborn animals studied by Karunairatnam, Kerr and Levvy,[17] Hartiala and Pulkkinen,[18] Brown, Zuelzer, and Burnett,[19] and Vest [4c] in which they demonstrated an insufficient glucuronide formation by the liver during the newborn period.

In connection with our investigations we would like to draw attention to the fact that acetanilid, particularly in newborn infants, has the tendency to form methemoglobin. The amount of methemoglobin was generally held within justifiable limits, under 1 gm. %, by the small doses, 20 mg. per kilogram of body weight, of acetanilid used. In future experiments it might be preferable to substitute N-acetyl-*p*-aminophenol for acetanilid as a test substance, since it forms considerably less aniline in the blood and therefore much less methemoglobin is produced (Flinn and Brodie [20]).

Summary

N-acetyl-*p*-aminophenol is the oxidation product formed in the body after the absorption of an orally administered dose of acetanilid. The N-acetyl-*p*-aminophenol is conjugated with glucuronic acid to form N-acetyl-*p*-aminophenol glucuronide. We compared the course and speed of this glucuronide formation in newborn infants and older children by measuring the blood concentrations of these compounds.

In newborn infants the formation of the glucuronide was found to occur at a greatly retarded rate.

The study shows that evidently the glucuronic acid transferase, localized in the liver cells, is not completely developed in the newborn infant.

The importance of this finding for the pathogenesis of icterus neonatorum is discussed, with the fact in mind that it is also necessary for bilirubin to be conjugated with glucuronic acid before it can be excreted.

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An Exchange Transfusion Formula

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Introduction

The purpose of this paper is to present a simple formula permitting rapid calculation of the following data essential to the performance of an exchange transfusion for an infant, child, or adult: (*a*) the volume of donor blood needed; (*b*) the length of time required to perform the exchange transfusion; (*c*) the number of "unit exchanges" required; (*d*) the per cent exchange effected.

The formula will be presented after a discussion of background material essential to its effective application. Four typical problems are then discussed, followed by a summary. Derivation of the formula and related subjects are given in an appendix.

The Exchange Transfusion

Since 1946 the exchange transfusion has become the accepted method in treatment of erythroblastosis fetalis.[1-3] Since 1950 exchange transfusions have been used to treat blood transfusion reactions[4] and poisoning when conventional methods have failed. Poisoning by the following substances has been treated successfully by exchange transfusions: chloramine-T,[5] boric acid,[6] salicylates,[7,8] isoniazid,[9] phenylbutazone (Butazolidin),[10] and a combination of barbiturate and belladonna derivatives.[11] Application of the exchange transfusion technique beyond the newborn period has created the need for the formula to be presented.

The formula presented applies to both types of exchange transfusion in use—the "continuous" exchange transfusion and the "interval" exchange transfusion. A continuous exchange transfusion takes place when blood is continuously removed from the blood stream at a constant rate while fresh blood is simultaneously restored to the blood stream at the same rate.

An interval exchange transfusion takes place when a "unit exchange" is performed repeatedly. A unit exchange consists of drawing out a small but constant volume of blood from the patient by means of a calibrated syringe and replacing it with an equal volume of fresh blood. The interval exchange transfusion will constitute the major subject of discussion of this paper since it is most commonly used. The formula given, however, applies to both continuous and interval exchange transfusions. The quantitative relation of the two types of exchange transfusions will be discussed in an appendix.

If enough unit exchanges are performed, up to 90% of the patient's blood may be replaced by fresh blood. More than a 90% replacement is not practical because the number of unit exchanges and the volume of donor blood required become too large. Erythroblastosis fetalis, poisoning,[7] and transfusion reaction[4] have been treated successfully by exchange transfusions which replaced only 40% of the patient's blood volume. Hence the upper practical limit of an exchange transfusion is 90% and the lowest effective level is probably in the neighborhood of 40%.

When the exchange transfusion is completed, poison will continue to flow from the interstitial space into the blood stream. Any poison left in the gastrointestinal tract, after gastric lavage, will also add to the blood level of poison after the exchange transfusion is completed. The flow of poison into the blood stream will continue until equilibrium is reestablished between the concentrations of poison in the regions

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mentioned. In general, then, there will nearly always be a rise in the blood level of the poison one wishes to remove from the body, after the exchange transfusion. If the blood level of the toxic substance rises above a critical value, a repeat exchange transfusion may be necessary. A delay in performing a needed repeat exchange transfusion may permit irreversible damage to the patient's vital centers.

Calculation Procedure

The exchange transfusion formula to be discussed is

$$nv = K_{\%E} V$$

where n = the number of unit exchanges employed; v = the volume of the syringe used, in cubic centimeters; V = the patient's blood volume, in cubic centimeters, and $K_{\%E}$ = a constant dependent on the per cent exchange performed, and for that per cent exchange only (see Table for values of $K_{\%E}$ as a function of the per cent exchange performed). The formula is an approximation; its range of validity is discussed in an appendix. For the discussion below it is sufficiently accurate.

Corresponding to Various Per Cent Exchanges Calculation Procedure: Values of $K_{\%E}$

% Exchange Performed	$K_{\%E}$
90	2.303
80	1.609
70	1.204
60	0.9163
50	0.6932
40	0.5108
30	0.3567
20	0.2231
10	0.1054

It is clear that solution of exchange transfusion problems requires that the patient's blood volume V be known. If a direct measurement of the patient's blood volume by the Evans blue dye or radioactive tracer method is not available, one must use the average values described in the literature. There is some disagreement on these values.[12] For the purpose of this paper, the blood volume per unit weight of the patient has been taken to be 80 cc. per kilogram (K).

Four examples illustrating the use of the formula are discussed below.

1. A poisoned 2-year-old child weighing 11.3 K was treated by an exchange transfusion using 500 cc. of donor blood. At this point he returned to consciousness, and the exchange transfusion was stopped owing to technical difficulties. What per cent exchange was effected?

(*a*) $nv = K_{\%E} V$

(*b*) Although n and v are not given separately, the product nv must equal the volume of donor blood used, equal to 500 cc. in this case.

(*c*) Since the patient weighs 11.3 K, his blood volume is

$$V = (80 \text{ cc/K})(11.3 \text{ K}) = 904 \text{ cc.}$$

(*d*) Substituting in relation (*a*), one finds

$$500 \text{ cc.} = (904 \text{ cc.})\, K_{\%E}$$

$$K_{\%E} = 500/904 = 0.553$$

corresponding to an exchange transfusion of somewhat more than 40% (Table).

2. A 3.5 kg. infant needs a 90% exchange transfusion. How long will it take to perform using a 20 cc. syringe? How many units of donor blood will be needed?

(*a*) $nv = K_{\%E} V$

(*b*) $v = 20$ cc.

(*c*) $V = (80 \text{ cc/K})(3.5 \text{ K}) = 280$ cc.

(*d*) $K_{\%E} = 2.303$

since a 90% exchange is to be performed (Table).

(*e*) Substituting in (*a*), one finds

$$20n = (280)(2.303) = 644.8$$

$$n = 644.8/20 = 32.2 \text{ unit exchanges}$$

Since n must have integer values, one chooses $n = 32$ unit exchanges.

(*f*) It is found that a unit exchange using a 20 cc. syringe takes two minutes, while a unit exchange using a 10 cc. syringe takes one minute to perform.* Hence

(32 unit exchanges) (2 minutes/unit exchange) = 64 minutes = 1 hour and 4 minutes.

(*g*) The total volume of donor blood used is equal to nv, and this volume is calculated to be

$$nv = (32)(20) = 640 \text{ cc.}$$

(*h*) If one unit of donor blood contains 500 cc., then

$$nv/500 = 640/500 = 1.28$$

* The time taken to perform a "unit exchange" with either a 10 cc. or 20 cc. syringe could be reduced if polyethylene tubes and siliconized syringes were available and if the patient's blood were heparinized.

units of donor blood are required for the exchange transfusion.

3. This problem is designed to illustrate the use of the formula in deciding the relative values of an exchange transfusion or artificial kidney [13] for a given patient. Since the artificial kidney has an operational time of about four hours and the smallest effective exchange transfusion is in the neighborhood of 40%,† the problem is stated thus:

What is the greatest volume of blood for which one can perform a 40% exchange transfusion in four hours, using a 20 cc. syringe?

(*a*) $nv=VK_{\%E}$

(*b*) $v=20$ cc.

(*c*) Since a unit exchange occupies two minutes, when using a 20 cc. syringe, one can perform

$$n=(4 \text{ hr.})\ (60 \text{ min/hr.})/2 \text{ min.}=120$$

unit exchanges in four hours.

(*d*) Since a 40% exchange is planned, one finds $K_{\%E}=0.5108$ from the Table.

(*e*) Substituting in relation (*a*),

$$(120)\ (20 \text{ cc.})=(0.5108)\ V$$

$$V=(120)\ (20)/0.5108=4{,}700 \text{ cc.}$$

(*f*) A patient with a blood volume of 4,700 cc. would weigh approximately 4,700/80=59 K, this being about the weight of a 16-year-old.

(*g*) The number of units of donor blood required would be (one unit=500 cc.)

$$(120)\ (20)/500=4.80$$

units of donor blood.

Thus a 40% exchange transfusion can be done within four hours even for a patient with as large a blood volume as 4,700 cc. If a 40% exchange is deemed inadequate because of the patient's condition or the blood concentration of poison, the artificial kidney could be used. Because of technical problems the artificial kidney cannot be used on small children. In poisoned children too small to be treated by the artificial kidney, exchange transfusion may be employed to great advantage, as the next problem illustrates.

4. What is the oldest patient for whom a 90% exchange transfusion can be performed in six hours (four to six hours being the maximum time interval a team could perform an exchange transfusion) using a 20 cc. syringe?

(*a*) $nv=K_{\%E}V$

(*b*) $n=180$ (see 3c)

(*c*) Since a 90% exchange is planned,

$$K_{\%E}=2.303 \text{ (Table)}$$

(*d*) Substituting in (*a*):

$$(180)\ (20 \text{ cc.})=2.303\ V$$

$$V=1560 \text{ cc.}$$

(*e*) A blood volume of 1,560 cc. corresponds to a patient weighing 1560/80=19.5 K, the weight of a 5-year-old.

By a similar calculation, one finds that a team working four hours could carry out a 90% exchange transfusion in a patient weighing 13.0 K (about the weight of a 2.5-year-old).

† In any patient one would aim toward a 90% exchange if it could be obtained with the donor blood available and the equipment on hand; nevertheless 40% exchanges have saved lives.

Summary

A formula, $nv=K_{\%E}V$, is described which permits rapid calculation of essential data for exchange transfusions carried out at any age, without the use of logarithmic tables, calculus or exponents.

The terms of the formula are defined and the values for $K_{\%E}$ corresponding to various per cent exchanges are given in the Table.

The formula is specifically designed for use with the interval type exchange transfusion (Diamond technique), but may also be used for a continuous type exchange transfusion.

A background discussion essential for proper application of the formula is presented.

Four problems representing typical uses of the formula are discussed in detail.

The derivation of the formula and an evaluation of its accuracy is relegated to an appendix.

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Appendix

The formula $nv = K\%_{E}V$ is derived as follows: Let V = volume (cc.) of the patient's blood; v = volume (cc.) of the syringe used to perform the exchange transfusion; G_0 = the number of grams (gm.) of poison in the blood at the beginning of the exchange; C_0 = concentration (gm/cc.) of poison in the blood at the beginning of the exchange (by definition, $C_0 = G_0/V$); G_1 = number of grams of poison in the blood after the first unit exchange; C_1 = concentration of poison in the blood after the first unit exchange (by definition $C_1 = G_1/V$); G_2 = number of grams of poison in the blood after the second unit exchange, etc.

One can calculate C_1 in terms of C_0, v, and V by noting that

$$G_1 = C_0V - C_0v = C_0(V - v) \qquad (1a)$$

and since

$$C_1 = G_1/V$$

it follows that

$$C_1 = C_0(1 - v/V) \qquad (2a)$$

Similarly, one can show that

$$C_2 = C_1(1 - v/V) \qquad (3a)$$

whence, from (*2a*), it follows that

$$C_2 = C_0(1 - v/V)^2 \qquad (4a)$$

Again, one finds

$$C_3 = C_0(1 - v/V)^3 \qquad (5a)$$

etc., so that, in general

$$C_n = C_0(1 - v/V)^n \qquad (6a)$$

or

$$C_n/C_0 = (1 - v/V)^n \qquad (7a)$$

where n is an integer denoting the number of unit exchanges and C_n the concentration of poison in the blood after n unit exchanges.

Formula (*7a*) is an exact relation, but for calculational purposes it is more convenient to use an approximate expression obtained in the following way:

Taking the logarithm to the base e ($e = 2.71828\ldots$) of both sides of (*7a*), one finds

$$\log_e C_n/C_0 = n \log_e(1 - v/V) \qquad (8a)$$

If the ratio v/V be much less than unity, one can replace the logarithm in (*8a*) by the first term in its series expansion

$$\log_e(1 - v/V) = -v/V - (1/2)(v/V)^2 - (1/3)(v/V)^3 - \qquad (9a)$$

with an error no greater than the sum of the series

$$-(v/V)^2 - (v/V)^4 \ldots$$
$$= -(v/V)^2/(1 - v/V) \qquad (10a)$$

Since the largest value of v/V to be encountered is less than 1/20, the error in using the first term of the series is no more than about 0.05 of this term. And since a constant watch must be kept on the patient's clinical condition, an error of 5% is well within the margin of error permissible. In general, the error committed in the approximation is usually far less than 5% of the first term in (*9a*).

Making the indicated substitution in (8*a*), one finds

$$\log_e C_n/C_o=-nv/V \qquad (11a)$$

approximately. Setting

$$\left.\begin{aligned} K_{\%E}&=-\log_e C_n/C_o=+\log_e(C_o/C_n)\\ &=\log_e \frac{100}{100-\%\text{ exchange}}\end{aligned}\right\} \qquad (12a)$$

it follows that

$$nv=K_{\%E}V, \qquad (13a)$$

which was to be derived.

It is of interest to show the relation of formula (*7a*) to formulas given in the literature for continuous exchange transfusion by Wiener and Wexler.[14]

In the latter case, one may imagine an effectively infinite number of unit exchanges performed an effectively infinite number of times, so that while n approaches infinity and v approaches zero, the product nv approaches v_e, the total volume of donor blood used. Then, from the definition of the number e

$$e=\lim_{n\to\infty}(1+1/n)^n, \qquad (14a)$$

and (*7a*) one finds

$$\lim_{\substack{n\to\infty\\ v\to 0}}(1-v/V)^n=\lim_{n\to\infty}\left[\left(1-\frac{v_e}{nV}\right)^{-\frac{nV}{v_e}}\right]^{-\frac{v_e}{V}}$$

$$=e^{-(v_e/V)}$$

so that

$$C/C_o=e^{-(v_e/V)} \qquad (15a)$$

where C is the final poison concentration in the blood.

One notes, in reference to (*15a*), one may write

$$\log_e C/C_o=-v_e/V \qquad (16a)$$

whence, setting

$$K_{\%E}=-\log_e C_o/C_n \qquad (17a)$$

one finds

$$v_e=K_{\%E}V \qquad (18a)$$

exactly. Relation (*18a*) has a meaning identical with the approximate formula featured in the preceding paper.

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Needle Biopsy of the Liver

An Aid in the Differential Diagnosis of Prolonged Jaundice in Infancy

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The differential diagnosis of infants with prolonged obstructive jaundice is usually puzzling and often in error.[1] The differentiation between obstruction to the outflow of bile on the basis of hepatocellular disease and that due to atresia of the extrahepatic bile ducts is made difficult by a variety of factors. Among these are the frequency with which hepatitis leads to prolonged, essentially complete obstruction to the outflow of bile into the intestinal tract,[2,3] the poor correlation between the results of the commonly used tests for hepatic parenchymal cell damage (flocculation, turbidity[1] and transaminase tests[5]), and the disease process affecting the patient. The unreliability of histories concerning the time of onset of jaundice and the character of stool color,[1] as well as the results of chemical tests for bile pigments in urine and stool, may also lead to error in diagnosis.[1,4]

These facts have been more or less recognized in the past. Some workers have placed greatest reliance on the serial determination of serum bilirubin.[1,6] In general, patients in whom the obstructive process is the result of hepatocellular damage exhibit initially high values with a tendency toward an irregular downward trend with time. Patients with biliary atresia show lower values early in their course, with a tendency toward a steady, gradual rise in the serum bilirubin concentration. While this picture corresponds to the facts for fairly large groups of subjects, the changes with time of serum bilirubin concentration of individual patients may depart strikingly from the average for individuals with the particular entity from which the patient suffers.

In addition to the fact that serial bilirubin determinations may be misleading in individual subjects, inconclusive laboratory findings may result in delays in definitive diagnosis which may permit the development of an advanced cirrhotic condition in young infants.[1,6]

The observation of a 3-month-old infant who had already developed ascites, esophageal varices, and biliary cirrhosis secondary to atresia of the bile ducts has emphasized to us the need for early accurate diagnosis and definitive treatment in prolonged obstructive jaundice in infants. Of similar importance is the experience in this clinic that the only entirely curative results achieved in the treatment of biliary atresia were in infants upon whom operation was carried out prior to the age of 2 months.[7] On the other hand, there are considerations which lead to temporization in arriving at a definite diagnosis. There is a justifiable reluctance to subject the infant who may be suffering from hepatitis to the risks entailed in exploratory laparotomy, particularly in the early stages when spontaneous cure is most likely.[1,3] While the risks of limited exploration and cholangiography may not be great, sound clinical judgment will take into consideration the fact that the bulk of the survivors among infants with prolonged jaundice will come from those suffering from hepatitis and not from the relatively few with operable atresia of the bile ducts.[1,6,8]

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With these considerations in mind, an evaluation of needle biopsy as a diagnostic aid was undertaken, recognizing that its failure to achieve general use in this situation reflected adverse opinions as to its safety and diagnostic value. It was hoped that the procedure might prove safe and offer a means of arriving at an early definitive diagnosis.

This expectation has been realized in a majority of 25 cases of prolonged jaundice in infancy. Encouragement in using the needle biopsy technique was derived from reports of 581 biopsies in infants and children with nutritional disorders of the liver with only one serious complication [9-11] and by the subsequent report of Bruton,[12] who carried out 59 biopsies in infants and children with a variety of hepatic disorders without untoward event. It should be pointed out that the risks involved in puncturing an inflamed liver might exceed those encountered in the clinical material of the authors mentioned above.

Biopsy Technique

Needle biopsy employing the Vim-Silverman needle was carried out under local anesthesia only in subjects in whom hemoglobin concentration, prothrombin, bleeding, and coagulation times were found to be relatively normal. Feedings were withheld for approximately four hours before carrying out the procedure. The infants were given pentobarbital in a dosage of 15 to 60 mg. one-half hour before the biopsy. They were restrained by adhesive strapping across the upper thighs and chest. The skin was cleaned with benzalkonium (Zephiran) solution 1:1,000, and the subject was draped with sterile towels. An assistant was employed to steady the patient's shoulders and upper trunk. In all but a few of the subjects studied, the liver was sufficiently enlarged to make a transabdominal approach feasible. A transcostal route was used in the remaining subjects. The skin and musculature were infiltrated with 2-4 cc. of 1% procaine solution. To facilitate introduction of the needle, a 2-3 mm. incision is made through the skin at the midaxillary line, midway between the costal margin and the lower border of the liver. The needle, with stylet in place, is inserted into the liver in a cephalad direction at an angle of about 60 degrees from the long axis of the body in order to avoid the large vessels at the hilum. The insertion into the liver to a depth of about 1 cm. is made rapidly to avoid cutting the capsule of the liver with the needle edge. The stylet is withdrawn and replaced by the obturator, which is then inserted its full length into the liver, a distance of about 1.5 cm. beyond the edge of the needle. As the obturator is advanced its flexible hemicylinders are separated. The needle is then advanced over the obturator, and the tissue is firmly held. The entire assembly is rotated 360 degrees to sever the core of tissue from its attachment and then withdrawn. The skin incision is covered with a dry dressing. The patient is observed for general condition, including pulse and respiratory rates at 15-minute intervals, for the next two hours and less frequently for an additional two hours.

In no instance was it necessary to call upon a surgical "rescue squad" to deal with bleeding. In one patient with hepatitis, free blood was found in the peritoneum at laparotomy, and a fall in hemoglobin of 2 gm. was noted.

Details of Fixation.—Single needle biopsy specimens were routinely placed in a modified Carnoy's fluid (three parts of absolute alcohol and one part of glacial acetic acid). After fixation, the tissue was dehydrated and paraffin embedded. Serial sections at 5μ were utilized for routine hematoxylin and eosin stains. When indicated, the PAS and aniline blue chromotrope methods were employed.

Material

All biopsies attempted in infants with prolonged jaundice are included in this report. Most of the first 17 biopsies were done by members of the resident staff supervised by one of us. In an effort to decrease the proportion of unsatisfactory specimens obtained (6 of 17), the last 8 biopsies were done by R. K. with a decrease in unsatisfactory specimens to 1 of 8. Later in the study, as more confidence in the safety of the procedure was gained, second attempts were made when the first biopsy specimen appeared unsatisfactory.

The subjects of the present report are 25 infants between the ages of 3 weeks and 18 months.

TABLE 1.—*Age of Patients on Admission*

Age, Mo.	No.
1	5
1-2	6
2-3	5
3-5	3
5-9	2
9-18	4
Total	25

The age distribution of the patients on admission is given in Table 1. With the exception of three infants, all were admitted to The Children's Hospital of Philadelphia. Two infants were studied at the request of Drs. Paul Gyorgy and Lewis Barness, one at the Philadelphia General Hospital and the other at the Hospital of the University of Pennsylvania. The third infant was studied at the Driscoll Foundation Children's Hospital, Corpus Christi, Texas, at the request of Dr. Joseph M. Sloan.

Criteria for Histologic Diagnosis

Accurate histologic diagnosis, for the purpose of differentiating biliary atresia from hepatitis, requires samples of liver tissue which include portal as well as hepatic parenchymal cell areas. In biliary atresia, the important findings are (1) marked increase in fibrous tissue in the periportal areas; (2) proliferation of bile ducts; (3) intraductal bile stasis, and (4) maintenance of liver cord pattern. Of these criteria, most importance is attached to the first two, as tissue obtained from patients with biliary atresia may exhibit small numbers of inflammatory cells in the portal areas and a few multinucleated giant cells among the parenchymal cell cords.

Figure 1 shows typical findings obtained in a needle biopsy specimen of an infant aged 4 months with proved atresia of the extrahepatic bile ducts. The increased fibrous tissue in the periportal area, proliferation of bile ducts, maintenance of the liver cord pattern, and normal appearance of the hepatic parenchyma are evident.

A histologic diagnosis of hepatitis is made on the following findings similar to those described by Craig and Landing [13]: (1) distortion of the lobular architecture by swollen parenchymal cells, many of which are multinucleated giant cells; (2) minimal or absent bile duct proliferation and fibrosis in the portal areas. Bile stasis in the intercellular canaliculi and the parenchymal cells is usually apparent, and lymphocytes are frequently observed in the portal areas. In severe cases of hepatitis, there may be almost complete transformation of the parenchyma into swollen or multinucleated giant cells, and focal accumulations of inflammatory cells may be noted. Figure 2 illustrates this type of alteration in a 4-month-old infant with hepatitis.

Occasionally a specimen which is adequate according to the criteria mentioned above will not be sufficiently characteristic to permit one to make a definitive diagnosis. One such instance was encountered in the present series, as mentioned later.

All specimens obtained by needle biopsy will not yield material adequate for diagnostic purposes. In general, specimens of 6 mm. or more in length will prove to be suitable. Biopsy material which does not provide examples of both portal and parenchymal areas should be read as "inadequate for diagnosis."

As will be discussed below, specimens which do not yield portal areas for examination will not permit exclusion of biliary atresia; however, they may show sufficiently marked changes in hepatic parenchyma to justify further observation prior to laparotomy.

Table 2 shows the results from the standpoint of adequacy for diagnostic purposes in 25 successive cases of prolonged jaundice.

The over-all adequacy of needle biopsy specimens in this series is 72%. As pointed out above this is lower than can be obtained when the operator has gained skill with experience. Seven of the last eight biopsies (87.5%), done by one of us, resulted in obtaining material suitable for histologic diagnosis.

TABLE 2.—*Adequacy of Needle Biopsy Specimens in Twenty-Five Cases of Prolonged Jaundice*

	Adequate	Inadequate	Total
Biliary atresia	12	2	14
Hepatitis	6	5	11
Total	18	7	25

Contribution of Needle Biopsy to the Management of Individual Patients

Data obtained by needle biopsy proved to be of considerable value in a majority of the patients. In the group with biliary atresia, 12 of 14 biopsies yielded diagnostic material. There were findings in five of these subjects in the history or laboratory examination which made hepatitis the most probable diagnosis. In these patients, histologic examination led to the correct diagnosis, which was confirmed by surgical exploration. The clinical findings in the other seven subjects were consistent with the diagnosis of biliary atresia, and the biopsies were merely confirmatory. Most of these latter patients were referred directly to the surgical service for exploration, the diagnosis of biliary atresia having been made. Before much experience with the diagnostic value of needle biopsy had been obtained, the decision to explore some of these subjects was reached on the basis of clinical and laboratory evidence alone.

Of considerable interest from the standpoint of the diagnostic value of needle biopsy are the five patients with proved atresia of the bile ducts and certain findings more suggestive of hepatitis. The misleading findings are tabulated in Table 3.

The illness in Patient A appeared to be hepatitis because the initial serum bilirubin level of 16.1 mg. % obtained at 7 weeks of age was higher than is usually seen in biliary atresia at this age and in addition exhibited a progressive fall to 6.1 mg. % at 17 weeks. In further support of the diagnosis of hepatitis was the presence of urobilinogen in a single stool analysis. During the period of observation, this diagnosis was questioned because of the development of a degree of hepatic induration which seemed more compatible with biliary cirrhosis secondary to atresia of the bile ducts. The decision to attempt the first needle biopsy in this series was undertaken because of reluctance to subject a patient with severe hepatitis to the potentially adverse effects of anesthesia and exploratory laparotomy. The needle biopsy specimen, shown in Figure 1, revealed the bile duct proliferation and portal fibrosis diagnostic of biliary atresia. Cholangiography at operation, as described by Harris, O'Hara, and Koop,[14] showed the hepatic ducts to be atretic while the distal ducts were patent. The patient did fairly well postoperatively but began to fail in a few months and died at the age of 22 months. Autopsy confirmed the operative diagnosis.

TABLE 3.—*Misleading Findings in 5 Cases of Biliary Atresia with Diagnostic Needle Biopsies*

Patient & Age at First Examination	History		Laboratory		
				Urobilinogen	
	Onset Jaundice	Stool Color	Serum Bilirubin	Stool	Urine
A 6 wk.			Falling 16.1 mg. %- 7 wk. 6.1 mg. %-17 wk.	+	
B 15 mo.	Intermittent 5-10 days 4- 9 mo. 14-15 mo.	Variable, with jaundice			
C 2.5 mo.	2 mo.	Brown, becoming white		+	+
D 3 wk.		Yellow, becoming white	Increasing 9.8 mg. %-3 wk. 19.5 mg. %-6 wk.		+
E 7 wk.	6 wk.	Yellow, becoming white	Increasing 8.7 mg. %-7 wk. 14.0 mg. %-9 wk.		

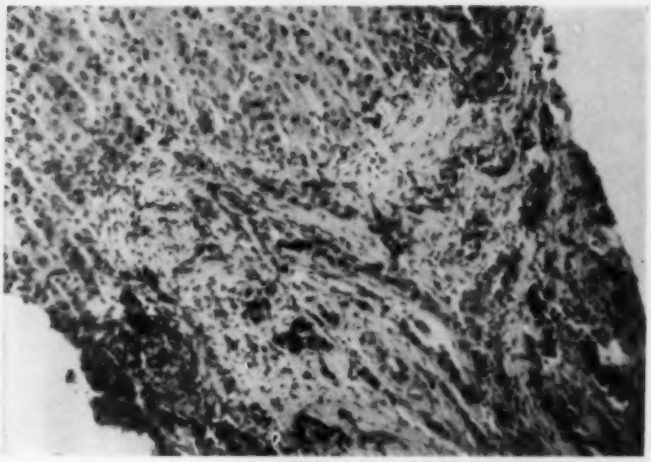

Fig. 1.—The maintenance of the liver cord pattern and normal appearance of the hepatic parenchyma are seen. Numerous bile canaliculi are imbedded in fibrous tissue extending outward from the portal area. (Reduced about 40% from mag. × 100.)

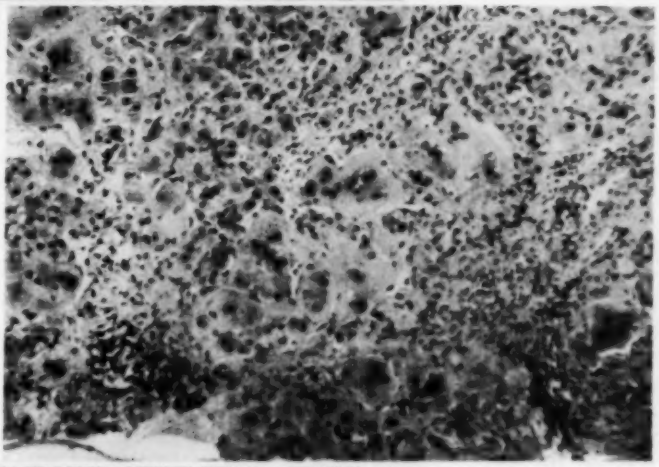

Fig. 2.—The parenchymal cells of the liver are transformed almost entirely into multinucleated giant cells. Numerous inflammatory cells are seen throughout the section. (Reduced about 40% from mag. × 100.)

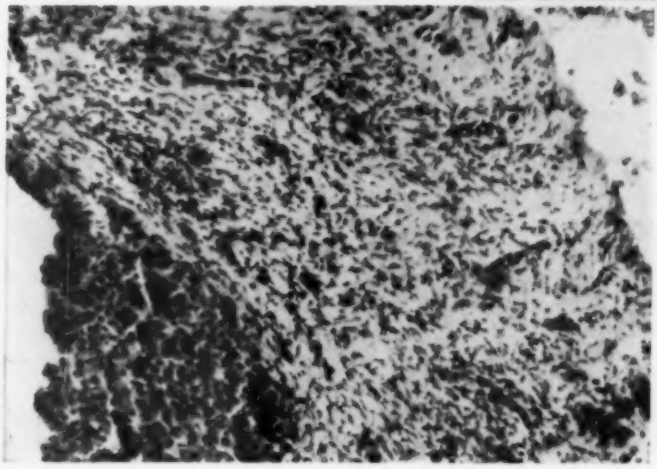

Fig. 3.—The relatively normal appearance of the liver cells is apparent. The remainder of the section consists of a broad band of fibrous tissue in which there are many collapsed bile canaliculi. (Reduced about 40% from mag. × 100.)

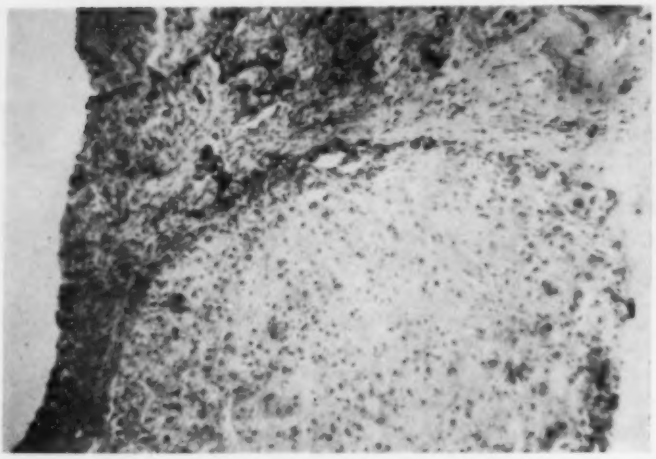

Fig. 4.—The striking feature of this section is the dense band of fibrous tissue extending out from the portal area surrounding the periphery of a lobule. Numerous proliferating bile canaliculi are imbedded in the fibrous tissue. The cord-like pattern is not as well maintained as in the usual case of biliary atresia. (Reduced about 40% from mag. × 60.)

Patient B was first seen at the age of 15 months. Except for moderate icterus and a markedly enlarged and indurated liver, she appeared to be in fairly good health. Her history suggested that she suffered from a chronic hepatitis in that there had been three distinct episodes of jaundice and pale stools, and intervals between these episodes in which she was free of jaundice and passed stools of normal color. The needle biopsy specimen, shown in Figure 3, demonstrated massive fibrosis and proliferation of bile ducts.

Cholangiography showed atresia or marked stenosis of the distal portion of the common bile duct with extreme dilatation of the intra- and extrahepatic bile ducts. Surgical repair was successful, but the far-advanced biliary cirrhosis suggests an ultimately poor prognosis.

The most probable diagnosis in Patient C seemed to be hepatitis in view of a history of late onset of jaundice at 2 months and of stools which changed in color from brown to white. This impression was strengthened by positive tests for urobilinogen in both urine and stool. However, examination of tissue obtained by needle biopsy revealed the histologic findings of biliary cirrhosis as shown in Figure 4. Unfortunately, laparotomy revealed the extrahepatic biliary tree to be reduced to atretic cords.

Patient D, who was studied initially at 3 weeks of age, appeared to be suffering from hepatitis because of the history of onset of jaundice at the age of 3 weeks along with change in stool color from yellow to white. In addition, serum bilirubin rose from 9.8 mg. % at 3 weeks to 19.5 mg. % at 6 weeks. An abrupt increase in concentration of serum bilirubin is more likely to occur in hepatitis in contrast to the slow, steady rise noted in subjects with biliary atresia. In addition, a positive test for urobilinogen was obtained in the urine. In spite of all of these findings which suggested that hepatitis was the underlying problem, tissue obtained by needle biopsy revealed the presence of biliary cirrhosis. A completely atretic extrahepatic biliary tract was found at operation.

The findings in Patient E were similar, with a history of late onset of jaundice at 6 weeks accompanied by a change in stool color from yellow to white and an abrupt increase in serum bilirubin concentration from 8.7 mg. % at 7 weeks to 14.0 mg. % at 9 weeks. Tissue obtained by needle biopsy, shown in Figure 5, presented typical findings of biliary cirrhosis; marked fibrosis, and minimal parenchymal cell alterations. Operation disclosed a completely atretic extrahepatic biliary tract.

A further indication of the potential value of needle biopsy in arriving at an

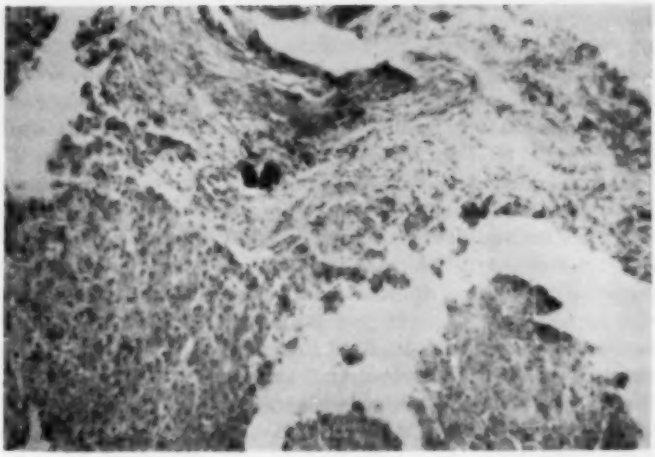

Fig. 5.—Note relatively normal parenchyma, the dense fibrous scar extending outward from the portal area at the periphery of the lobule and bile "thrombus" in bile duct. Hyperplasia of biliary ductal structures is not prominent in the section. (Reduced about 40% from mag. × 60.)

early diagnosis of biliary atresia is shown in Figure 6. This specimen was obtained from a jaundiced infant (F) at the age of 3 weeks and shows the proliferation of bile canaliculi and increase in periportal connective tissue characteristic of this condition.

Needle Biopsy Findings in Infants with Hepatitis

Eleven infants with hepatitis have been subjected to needle biopsy. The number of inadequate specimens (5 of 11) was greater in these subjects than in those with biliary atresia (2 of 14). This may be related to the greater ease of grasping with the biopsy needle the more fibrous liver tissue of biliary cirrhosis in contrast to the apparently friable tissue of subjects with hepatitis. Another factor contributing to the increased incidence of failure among the hepatitis patients was undoubtedly the greater frequency with which a free flow of blood occurred when the stylet was withdrawn. Although the quantity of blood did not amount to more than about 1 ml. in any case, it suggested the possibility of more serious internal bleeding and influenced the operator to carry out the procedure hastily and also discouraged second attempts when

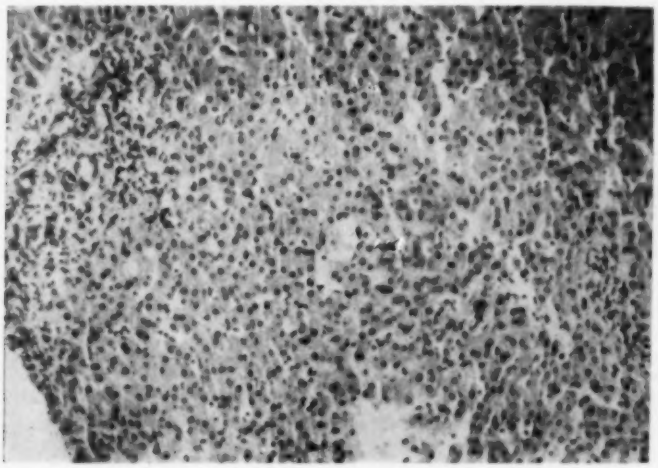

Fig. 6.—Normal hepatic cell parenchyma is apparent, with evidence of hyperplasia of bile canaliculi and moderate increase in periportal fibrous tissue. (Reduced about 40% from mag. × 100.)

the first appeared to yield an inadequate quantity of tissue.

It should be pointed out, however, that a biopsy specimen which must be considered "inadequate" according to the histologic criteria mentioned above may yield useful information in the management of a patient. An example of this was encountered in the case of Patient G, who was referred to the surgical service for exploration with a diagnosis of biliary atresia. At this stage of the study the needle biopsy was considered an investigational rather than a clinical diagnostic study, and laparotomy and cholangiography, which revealed patency of the intra- and extrahepatic bile ducts, were carried out before the biopsy specimen was examined. Within a few days of operation, the patient's jaundice began to clear, and he has since made a satisfactory recovery. The tissue obtained at biopsy was considered "inadequate" because it failed to provide portal areas for examination; however, the transformation of the parenchyma into large, swollen cells, compression of sinusoids, and the presence of many multinucleated cells made the diagnosis of hepatitis practically certain. Although this biopsy did not rule out the possibility of a concomitant biliary atresia, it was sufficiently diagnostic of hepatitis as to have delayed exploration for a further period, during which, in all probability, the jaundice would have cleared.

As experience with needle biopsy findings has been gained, the procedure has come to play a definite role in the management of patients with hepatitis. In three of the last four patients with hepatitis, diagnostic biopsy specimens have been obtained and operation has been withheld. Two of these patients are now clinically well and the third (H) is doing fairly well. His serum bilirubin level has fallen from an initial figure of 6.0 mg. % at the age of 4 months to 2.2 mg. % at the age of 6 months, and the liver has decreased in size.

A summary of the findings in these patients is given in Table 4. The presence of small amounts of urobilinogen was noted in the urine of all three of these patients and in the stool of one of the subjects.

TABLE 4.—*Summary of Hepatitis Patients Who Were Not Explored*

Patient	I		H		J	
Date of birth	11/8/57		1/24/58		8/1/57	
History and physical findings	Jaundice since birth; dark urine, normal stools; sibling jaundiced at birth, thin, liver and spleen 2 cm. enlarged		Jaundice since birth; dark urine, light stools; well nourished; liver 5 cm. and spleen 4 cm. enlarged		Intermittent, fluctuating jaundice since birth; stools acholic at times; urine dark; well nourished; liver barely palpable.	
Laboratory data	Date	1/7/58	5/26/58	7/24/58	10/15/57	10/26/57
	Bilirubin mg. %	17.5	6.0	2.2	4.3	6.9
	Transaminase (S-G-O) units	260	832	224	160	
	Cephalin flocc.	0	0	0	3+	
	Thymol turb. units	0.9	1.2		0.3	
	Phosphatase mg. %	12.	4.8	8.8	22.8	
	Cholesterol mg. %	240	220	184	172	
	Prothrombin % normal	80	45-100 *	70	80	
	Stool				2.4 E.U.†	
	Urobilinogen	0				
	Bile	±				
	Urine					
	Urobilinogen	1:10, 0	+1:10	+1:10	+1:10	
	Bile	+	+	+	0	
Outcome	Aug. 1958—doing well; no jaundice; liver not enlarged		Sept. 1958—not jaundiced; liver 2 fingerbreadths enlarged; on steroids		April, 1958—doing well; no jaundice; liver not enlarged	

* Following parenteral vitamin K.
† Ehrlich units.

While this finding is more typical of an incomplete obstruction due to hepatitis rather than the total obstruction of biliary atresia, it may be seen in three of our patients (Table 3) and in others reported in the literature[1,4] that small amounts of urobilinogen may be found in the urine or stools of patients with biliary atresia. Although a presumptive diagnosis of hepatitis was made in each of the three subjects, anatomical confirmation obtained by needle biopsy firmly established the basis for deferring exploratory laparotomy.

The severe giant-cell hepatitis found in Patient H is illustrated in Figure 2. The destruction of parenchymal cells, distortion of lobular architecture and presence of many multinucleated giant cells is striking and represents the severest example of hepatitis from the histologic standpoint encountered in the present study.

In I and J less severe processes were seen, with distortion of lobular pattern, degeneration of liver cells, some multinucleated giant cells and a marked infiltration of the portal areas by mononuclear cells.

In the remaining three patients with hepatitis whose slides were judged to be adequate from an anatomical standpoint, two patients were explored because of the extreme chronicity of their disease, and the third because of doubt as to the nature of the process revealed by histologic examination. In this subject, K, although portal and parenchymal areas were seen in the tissue obtained by needle biopsy a definite diagnosis could not be reached on the basis of the histologic findings. Operative biopsy revealed evidence of hepatitis, and cholangiography showed hypoplasia of the extrahepatic biliary tree with patent intrahepatic biliary radicles.

Comment

It is a fact, as pointed out by Gellis and Hsia,[6] that the differential diagnosis of prolonged jaundice in infancy can often be made correctly on clinical and laboratory study. In many instances, however, the diagnosis will be in doubt because of misleading findings which suggest the presence of an acquired hepatic disease with incomplete biliary obstruction when the patient's illness is the result of biliary atresia. Conversely, hepatitis may simulate biliary atresia as described by Harris et al.[2] The finding of urobilinogen or bilirubin in the stool or of urobilinogen in the urine was noted in 8 of 14 of the present series of patients with biliary atresia. Hsia and Gellis found 8 of 26 tests for urobilinogen in the urine positive in their patients with biliary atresia.[4] Norris and Hays[1] found positive tests for bile pigments in the stools in 4 of 48 patients and for urobilinogen in the urine in 4 of 27 patients with biliary atresia. The latter authors obtained a history of passing pigmented stools in 5 of 51 of their patients with biliary atresia.

It is clear that individual patients with biliary atresia may present certain findings more suggestive of the presence of hepatitis. The prolonged observation necessary to arrive at a fairly certain diagnosis may permit the development of advanced biliary cirrhosis, as in the patient mentioned above who succumbed with ascites and esophageal varices at the age of 3 months.

The hesitancy to subject the infant with hepatitis to exploratory laparotomy is strengthened by the report of Gellis, Craig, and Hsia that 10 of 16 infants with hepatitis died or developed cirrhosis after exploration, in contrast to similar sequelae in only 2 of 13 who were not explored.[3] Similar observations were presented by Norris and Hays, who noted cirrhosis or death in 6 of 8 infants with hepatitis who were surgically explored while only 1 of 15 infants developed cirrhosis among those who were not operated upon.

The considerations outlined above suggest that there is a need for additional diagnostic techniques in the management of infants with prolonged jaundice.

Needle biopsy appears to be a safe procedure when done in subjects with normal bleeding, coagulation, and prothrombin times, and to offer a means of arriving at

an early definitive diagnosis in most patients with prolonged jaundice. Diagnosis of biliary atresia in early infancy by this procedure should be accomplished in most instances. Diagnosis in F at 3 weeks, D at 6 weeks, C at 8 weeks, and E at 8 weeks is particularly noteworthy in this connection. None of these four patients proved to have operable anomalies. They do, however, illustrate the likelihood that prolonged observation in an effort to arrive at a diagnosis of biliary atresia may be avoided in most cases. Early diagnosis may avoid the development of biliary cirrhosis in those patients with operable anomalies.[1,6]

As experience was gained with the procedure, adequate biopsy specimens were obtained more frequently in patients with hepatitis. The findings in a biopsy judged inadequate by the criteria noted above may be sufficiently suggestive as to justify a few weeks delay in exploration during which interval an existing hepatitis may clear.

It is important to emphasize that a final diagnosis should not be made on specimens in which adequate examination of portal and parenchymal areas cannot be made. Such specimens should be reported as "inadequate for diagnosis." We encountered one instance in the present series in which biopsy material adequate by these criteria failed to yield findings which were sufficiently characteristic to arrive at a secure diagnosis. In this instance, the more ample tissue specimen obtained by operative biopsy revealed the disease process to be hepatitis.

Needle biopsy appears to be a valuable adjunct in the management of infants with prolonged jaundice. The findings obtained by its use may avoid the development of advanced biliary cirrhosis in the patient with an operable anomaly of the extrahepatic bile ducts, and spare the majority of patients with hepatitis unnecessary surgical intervention.

In those patients in whom exploratory laparotomy is indicated because of a definite diagnosis of biliary atresia or failure to establish hepatitis as the cause of jaundice, operative cholangiography permits accurate delineation of the anatomic state of the biliary ductal system with minimal operative and anesthetic trauma.[1,14]

Summary

Needle biopsy of the liver has been carried out in 25 infants aged 3 weeks to 18 months in whom normal bleeding, coagulation and prothrombin times had been determined. In 14 subjects the jaundice was secondary to biliary atresia and in 11 to hepatitis.

The technique of biopsy is described.

The histologic criteria for the differentiation of hepatitis and biliary atresia have been outlined.

According to the criteria described above, 12 of 14 biopsies in cases of biliary atresia and 6 of 11 biopsies in patients with hepatitis have been adequate for diagnosis.

In five patients, the correct diagnosis of biliary atresia was made on the basis of the biopsy specimen when certain findings were more suggestive of hepatitis.

The actual or potential value of needle biopsy in avoiding unnecessary laparotomy is described in four subjects with hepatitis.

Needle biopsy, by permitting early definitive diagnosis, may be an aid in avoiding the development of biliary cirrhosis in patients with types of biliary atresia amenable to surgical correction.

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Infection in Children Following Splenectomy for Traumatic Rupture

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Does splenectomy in children influence susceptibility to infection? Since 1952, when King and Schumacker [7] reported five cases of severe infection in infants following splenectomy, this question has been the subject of much controversy.[2-7,9,12,13] We are presenting a follow-up study of 33 apparently normal children who had splenectomy for traumatic rupture. This is an attempt to establish the incidence of acute sterile pericarditis, sepsis, meningitis, or any other severe infection especially when due to the Pneumococcus in this type of patient. Other authors [4-7,12] have reported a 4% to 28% incidence of these severe postsplenectomy infections in infants and children. Although the indication for operation varied, it was usually for some hematological disorder. Cooley's anemia was by far the commonest of these diseases. However, these series contained few cases of traumatic rupture. This paper deals only with the problem as it pertains to normal children who have had splenectomy for traumatic rupture.

Material

We have reported the clinical aspects and management of the cases comprising this series in a previous paper.[1] The 33 children were admitted to three New York hospitals in the years 1947 to 1958. Follow-up studies have been obtained in 26 children. We do not believe that the lack of follow-up on seven children is related to the problem, as must be assumed in cancer statistics, but merely reflects the difficulty of following cases treated in a municipal hospital. The ages at the time of splenectomy ranged from 2 to 15 years (Table 1). Antibiotics, when given, were not continued beyond the child's hospital stay. Parents were asked whether their children had any subsequent illness requiring a doctor's care.

TABLE 1.—*Age Distribution*

Age, Yr.	No. of Cases
3- 4	4
5- 6	6
7- 8	5
9-10	3
11-12	5
13-14	3

All 26 children were alive and well at the time of follow-up. With the exception of one child who received antibiotic therapy for a mild throat infection, none developed any severe infection. Specifically, there was no history of pneumonia, meningitis, pericarditis, or septicemia.

Comment

Sufficient evidence has been presented to suggest an increase in susceptibility to severe infection following splenectomy in children with preexisting disease (Table 3).

TABLE 2.—*Length of Follow-Up*

Time	No. of Cases
2- 6 mo	4
6-12 mo	3
1- 3 yr	8
4- 6 yr	4
7-10 yr	7

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TABLE 3.—*Incidence of Subsequent Infection in Follow-Up Series*

Authors	Preexisting Disease		Traumatic Rupture	
	No. of Cases	Subsequent Infection	No. of Cases	Subsequent Infection
Walter & Chaffin (1955)	62	2	10	0
Gofstein & Gellis (1956)	59	4	18	0
Huntley (1958)	44	7	2	0
Smith, et al. (1957)	50	14	0	0
McKinnon, et al.	0	0	26	0
Total	245	27 (11%)	56	0 (0%)

There is little proof, however, that such susceptibility occurs in normal children having splenectomy for traumatic rupture. The absence of any severe infection in our patients as well as in those cases of traumatic rupture of the spleen included in other follow-up studies (Table 3) suggests that splenectomy in the normal child does not increase his susceptibility to infection. Experimental evidence substantiating this impression is provided by Rothberg and Corallo [10] in their study on weaning and suckling rats. Splenectomy did not increase the animals' susceptibility to intraperitoneal injection of Pneumococcus as compared with control animals. Since preexisting disease was the indication for surgery in all but 2 of the 50 odd reported cases of postsplenectomy infection in children, the possibility exists that this susceptibility is related to the primary disease as well as to the removal of the spleen. Smith and his co-workers [12] reported a 28% incidence of serious infection in 50 children who had had splenectomy at the New York Hospital in the 10 years prior to the report. However, none of these children had splenectomy for traumatic rupture.[11] The two cases of infection in children following splenectomy for traumatic rupture which were included in their paper were taken from another institution. Such isolated case reports are of no statistical value in establishing the potential danger of splenectomy in normal children.

It has been suggested that antibiotic therapy be continued for as long as two years after splenectomy in children. In view of our findings this does not appear to be necessary in otherwise healthy children who require splenectomy for traumatic rupture. Similarly, some authors [8] have advocated suturing of lacerations of the spleen rather than splenectomy in order to avoid the loss of the protective function of this organ. The results of this study and the dangers inherent in such a procedure make this idea untenable.

In further evaluating the significance of our study, two factors should be considered. The first is the length of follow-up. The interval between splenectomy and infection has been reported to vary from one day [5,11] to 12 years.[11] However, the majority of patients developed infection within one year, and many within six months. We feel that the follow-up of two months to 10 years in this series is long enough for some evidence of increased susceptibility to infection to have become manifest. The second factor is the age of the patient at the time of splenectomy. Traumatic splenic rupture is extremely rare in the first and second years of life.[1] The significance of the age distribution of our patients must be considered in the light of two conflicting groups of reports. King and Schumacker [7] and Huntley [6] have found postsplenectomy infection to be more prevalent in infants, but Smith [11] and his co-workers and Gofstein and Gellis [4] have found an equal number of such infections in children over 2 years of age.

Summary

No increase in susceptibility to infection was found in 26 children who had had splenectomy performed for traumatic rupture. Follow-up periods ranged from two months to 10 years. The absence of infection in normal children is in contradistinction to the increased incidence reported following splenectomy for preexisting disease. Long-term antibiotic therapy follow-

ing splenectomy for traumatic rupture in children appears unwarranted.

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Occipital Dermal Sinus

Clinical and Radiological Findings When a Complete Occipital Dermal Sinus Is Associated with a Dermoid Cyst

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The purpose of this paper is to call attention to the high incidence of intracranial infection (meningitis, cerebral abscess) when a complete occipital dermal sinus is associated with a dermoid cyst. In addition, important clinical and radiological findings are stressed that should make one suspicious when this condition is present. The congenital dermal sinus represents a midline defect whereby the dermal sinus opening in the skin is connected by a tract to a dermoid cyst in the posterior fossa. This pathway is a direct source of intracranial infection. The sinus tract extending through the occipital bone causes a bony defect which can be diagnosed radiologically. These radiological findings were mentioned by Matson and Ingraham[2] in 1951 and later clarified by Logue and Till[3] in 1952. During the past 10 years 17 cases have been published (Table 1), to which we are adding two additional cases.

It is impressive to note the high incidence of intracranial infection in this condition before the proper diagnosis is made. This is of importance since the mortality and morbidity rates increase once the dermoid cyst or the central nervous system becomes infected. Infection makes surgery more difficult and increases the hazard of a postoperative meningitis or cerebral abscess (Case 2).

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TABLE 1.—*Cases of Complete Occipital Dermal Sinus with Posterior Fossa Dermoid Cyst Reported in the Literature During the Past Ten Years and Reviewed By the Authors* *

Authors	Year Reported	No. of Cases	Living & Well	Defective	Dead
Mount[1]	1949	2	1	—	1
Matson & Ingraham[2]	1951	8	4	2	2
Logue & Till[3]	1952	4	3	—	1
Tytus, & Pennybacker[4]	1956	2	1	—	1
Roberts[5]	1958	1	1	—	—
Present report	—	2	1	1	—
Total		19	11	3	5
Percentage			58%	16%	26%

* A few cases reported in the literature were not included because they did not meet our definition or the material published was insufficient for analysis.

Report of Cases

CASE 1.—This 7-month-old white boy was admitted to Variety Children's Hospital with a diagnosis of bacterial meningitis. He had a fever of four days' duration, and on the day prior to admission he received 300,000 units of procaine penicillin and 0.5 gm. of streptomycin by injection and a sulfonamide by mouth. Lethargy and nucal rigidity began the evening before admission to the hospital. Lumbar puncture done on admission to the hospital revealed a cloudy cerebrospinal fluid that contained 5,700 white blood cells which were mainly polymorphonuclear cells. The cerebrospinal fluid sugar was reduced in amount. No bacteria were seen on a smear of the fluid, and a culture failed to grow any bacteria.

In the hospital the child was treated with penicillin at a dosage of 500,000 units intravenously every three hours, chloramphenicol succinate intravenously, 100 mg. per kilogram divided into three doses, and sulfadiazine, 200 mg. per kilogram divided into three doses and given subcutaneously. After 48 hours he was afebrile and had improved clinically. At this time, the regimen was changed to oral medications, except for penicillin, which was given intramuscularly. Forty-eight hours later he again became febrile and showed signs and symptoms of an increasing in-

Fig. 1 (Case 1).—Occipital area of the scalp showing dermal sinus with a few coarse hairs protruding from the center.

Fig. 2. (Case 1).—Radiograph of the occipital part of the skull showing the channel and groove in the occipital bone.

Fig. 3. (Case 1).—Anteroposterior radiograph showing deformity of cervical vertebrae.

tracranial infection. Bilateral subdural punctures failed to demonstrate a collection of fluid. Careful examination of the posterior occipital area revealed a dermal sinus and a small tuft of hair protruding from the center (Fig. 1). Radiographs of the skull (Fig. 2) revealed a central rarefied area measuring 0.4 cm. in diameter in the midline of the occipital bone in the region of the inion. Contiguous with and extending superiorly from the rarefied area was a channel through the occipital bone, 0.4 cm. in width and 1 cm. long. The sides of the channel showed sclerosis of bone. Radiographs of the cervical spines (Fig. 3) showed multiple deformities of the vertebral bodies

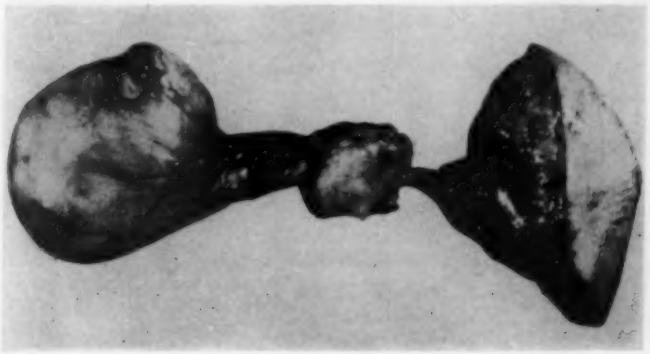

Fig. 4. (Case 1).—Dermal sinus opening in the skin with sinus tract leading through bone and terminating as a dermoid cyst.

and processes. Hemivertebrae, fused laminae, and a spinal bifida were present. These radiographic findings confirmed the fact that an intradural dermoid cyst was associated with the dermal sinus.

When the finding of a dermal sinus was explained to the parents they stated that shortly after birth a small swelling was noted over the midportion of the occipital scalp and that the hair matted in this area. The swelling and discharge in this area were not constant and recurred intermittently.

Antibiotics were continued for three weeks, after which time surgery was performed. At operation, the dermal sinus tract was exposed and found to run obliquely downward for 2 cm. At this point it passed through the defect in the bone. The bone surrounding the channel was removed to reveal the inner end of the sinus. An incision was made in the dura mater, and projecting into the cisterna magna was a thin-walled yellow, dermoid cyst measuring 2 cm. in diameter (Fig. 4).

Postoperatively a culture of the contents of the cyst grew Staphylococcus aureus. The organism was resistant to penicillin, but sensitive to chloramphenicol, erythromycin, tetracycline, and novobiocin. The cyst was lined by stratified squamous epithelium and filled with keratin and hairs. An inflammatory cellular infiltration was also noted.

Postoperative course was uneventful. The operation wound healed primarily, and the patient's development six months after the operation has been satisfactory, with no evidence of infection or hydrocephalus. It is of interest that an older sibling was born with a lumbar meningomyelocele, but no other central nervous system anomalies are known to exist in either of the parents' families.

CASE 2.—This 2-year-old boy was admitted to Variety Children's Hospital because of lethargy and nuchal rigidity. One week prior to admission he developed a fever and complained of a headache. The symptoms continued for four days, at which time he was seen by his family physician. The physician noted a midline occipital abscess, which he incised and drained. For the following three days the boy was given daily intramuscular penicillin and streptomycin and an oral sulfonamide. On the third day of treatment the patient developed nuchal rigidity and became lethargic. He was therefore referred to the hospital with the diagnosis of meningitis.

On admission to the hospital the boy was in a position of opisthotonos. Over the midline portion of the occipital area of the scalp there was a 2×2 cm. soft tissue swelling, with a sinus tract opening in the center. A bloody purulent drainage was coming from the sinus opening. Culture of this material grew a S. aureus. Cerebrospinal fluid

Fig. 5. (Case 2).—Radiograph of the occipital part of the skull showing the channel and groove in the occipital bone.

obtained by a lumbar puncture on admission to the hospital contained 193 white cells; 10% were polymorphonuclear cells, and 90% were monocytes. Cerebrospinal fluid sugar and protein were normal, and a culture failed to grow any bacteria. Radiographs of the skull (Fig. 5) showed a central rarefied area measuring 1.4 cm. in diameter in the midline of the occipital bone in the region of the inion. Contiguous with and extending superiorly from the rarefied area was a channel through the occipital bone 0.5 cm. in width and 1.2 cm. long. The sides of the channel showed sclerosis of bone. Radiographs of the cervical spine were normal.

During the next two weeks on a regimen of antibiotics the boy showed some clinical improvement, but suddenly began vomiting and developed papilledema. After this he convulsed and became lethargic. To relieve his increased intracranial pressure an emergency trephine procedure was done and bilateral ventricular drains inserted. Three days later an occipital craniectomy was performed, and an occipital intradural dermoid cyst was removed. Because of the location of the cyst surgery was difficult and the capsule was ruptured. Three weeks later a second occipital craniectomy was performed, and an occipital cerebellar abscess of the vermis was removed. The boy improved after these procedures, but later developed an increasing hydrocephalus. This was relieved by the insertion of a Holter valve. At the present time the boy has extensive central nervous system damage.

Embryology

Embryologically, the development of this abnormality has been explained as a defect resulting from misplacement of the fragments of ectoderm in the vicinity of the developing neural tube at about the third to fifth week of embryonic life. It is stated that failure of vagination of the primitive medullary plate to proceed in an orderly fashion results in a wide variety of defects involving the skin, central neuroaxis, and surrounding structures of mesodermal origin. Bremer [6] and recently Neuhauser et al.,[7] in his article discussing the features of neurenteric cysts, suggested that the neurenteric cyst may result from partial obliteration of the neurenteric or chorda canal. This is the canal which passes from the yoke sac through the primitive knot to the amniotic cavity, thus forming a communication from the gut to the dorsal surface of the embryo. The rare, but occasional, persistence of this canal would interfere with normal formation of midline structures and account for associated vertebral abnormalities. The possibility that this may represent the etiological defect explaining midline dorsal dermoid cyst with or without dermal sinus, neurenteric cyst, and diastematomyelia is advanced. The specific anomaly which is seen depends upon which portion of the neurenteric canal persists. It would seem to us that this is a more satisfactory explanation of the embryological defect than some others that have been proposed.

Roentgenography

The important radiographic finding when an occipital dermal sinus connects with an intradural dermoid cyst is a central rarefied area 1-2 cm. in diameter in the midline of the occipital bone in the region of the inion. Extending superiorly from the rarefied area is a short channel 1-1.5 cm. in length and 0.3-0.6 cm. in width and passing obliquely through the occipital bone in the midline. This is in contradistinction to the extradural dermoid cysts with a complete dermal sinus in which a smooth or scalloped circular defect of 1.5-5 cm. in diameter is observed. In the extradural dermoid cyst a channel is present in the bone, but cannot be demonstrated radiographically. Radiographs of the cervical vertebrae may show multiple deformities of the vertebral bodies and processes. Hemivertebrae, fused laminae, and spina bifida have been reported.

Diagnosis

Ideally the dermal sinus and dermoid cyst should be removed surgically before the cyst and the central nervous system become infected. However, the importance of an occipital dermal sinus or a midline occipital abscess was overlooked in seven patients (37%) of the cases reviewed. These patients had surgical drainage of a midline occipital scalp abscess sometime before the correct diagnosis was made. Some of these patients had repeated surgical drainage done on the scalp abscess when it refilled or

TABLE 2.—*Presenting Diagnosis* on Admission to Hospital*

	No. of Cases
Bacterial meningitis	8
Increased intracranial pressure	4
Cerebellar abscess	3
Abscess of occipital scalp	4
Total	19

* Denotes diagnosis on hospital admission when the dermal sinus and dermoid cyst were operated upon, since some of the children were hospitalized previously for meningitis or operated on for a local abscess of the occipital scalp.

failed to heal. Four patients had meningitis and one patient a cerebellar abscess drained at some time before the proper diagnosis was established.

It is also noteworthy that the presenting diagnosis, for the hospital admission during which the dermal sinus and dermoid cyst were diagnosed, was meningitis for eight patients (47%), increased intracranial pressure for four patients, and cerebral abscess for three patients (Table 2). It, therefore, becomes mandatory to look for a dermal sinus in any of these conditions. Since the sinus is small (Fig. 1) and may be well hidden by surrounding hair, it is wise to have good lighting and on occasion to shave the occipital area of the scalp. The sinus usually has a few hairs protruding from its center and a 1-2 mm. lack of hair surrounding the opening. Occasionally a sinus will be in the area of a port-wine stain. Extending from the sinus opening, a subcutaneous mass or a firm cord running obliquely downward may be palpated.

Sixteen patients at some time or other had evidence of intracranial infection (meningitis, cerebral abscess, or infected dermoid cyst). S. aureus was cultured in 11 of the cases (57%), Escherichia coli in 3 cases, and Proteus vulgaris (Bacillus proteus) and hemolytic Streptococcus in one case each. In one case both an E. coli and a hemolytic Streptococcus were cultured from the cerebrospinal fluid. Because of this high incidence of S. aureus with intracranial infection, whenever one is dealing with a patient with Staphylococcus meningitis a careful search for a dermal sinus should be made. The diagnosis is confirmed by the typical radiographic appearance.

Treatment

The treatment is surgical excision of the sinus tract and the dermoid cyst. This is best accomplished before intracranial infection occurs. Inflammatory reaction of the cyst capsule results in adhesions to the surrounding structures, making the removal of the cyst difficult and thus increasing the danger of rupturing the capsule and releasing the contents of the cyst intracranially. It is important to make every effort to remove the cyst intact, since Logue and Till [3] have shown that the bacteria will remain dormant within the cyst for months even though no evidence of active infection is present. Tearing the capsule at operation may introduce infection. Postoperatively, two cases of meningitis and one case of cerebellar abscess developed in the cases reviewed.

Five patients (26%) of the patients whose cases have been reviewed died as a result of intracranial infection, and three patients (16%) lived but were seriously physically handicapped as a result of their intracranial disease (Table 1). These complications also stress the need for making the diagnosis before intracranial infection occurs.

Comment

Both cases emphasize the importance of the dermal sinus as a source of intracranial infection (meningitis and cerebellar abscess) by S. aureus. The sinus tract provides direct access to the cavity of the dermoid cyst for bacteria on the surface of the skin. Once the intradural dermoid cyst becomes infected, the bacteria are separated from the cerebrospinal fluid only by the cyst lining and the pia-arachnoid. In contrast, the extradural dermoid cyst, because of its location, is less likely to lead to meningitis.

In the case of Patient 1 the dermoid cyst was removed intact and no postoperative infection developed, even though a S. aureus was cultured from the cyst after surgical removal. S. aureus could still be cultured from the cyst even though the patient received three weeks of intensive antibiotic therapy before surgery. It has been shown in other cases that bacteria will remain viable many months within these cysts. In Case 2, the dermoid cyst was ruptured during surgical removal because of technical difficulties. A postoperative cerebral abscess had to be removed three weeks later. Of the cases reviewed, two developed a postoperative meningitis. The surgical implication is apparent that careful removal of the intact dermoid cyst is essential in order to prevent contamination and reinfection of the central nervous system.

In both our patients the parents noted an intermittent discharge on the occipital part of the scalp that caused matting of the hair in this area. In the cases reported by other investigators, the sequence of events was similar to ours. In a patient with meningitis, or if one is suspicious that a dermal sinus exists, it should prove helpful to ask parents about matting of the hair or a midline swelling in the occipital area.

Both our cases confirm the diagnostic radiological findings of the occipital portion of the skull when an intradural dermoid cyst is associated with a dermal sinus. The radiological findings are different when an extradural dermoid cyst is present. These radiological findings enable the surgeon to know in advance where to expect the pathology and to be cognizant of the complications related to each position.

The association of this condition and anomalies of the cervical vertebrae are substantiated by our first case. These anomalies of cervical vertebrae probably have a common embryological basis with the dermal sinus and dermoid cyst. The relationship of the dermal sinus and cervical vertebrae anomalies in Case 1 to the lumbar meningomyelocele in the sibling is uncertain at the present time, but the fact that two central nervous system anomalies exist in these sibs may be of embryological importance.

Summary and Conclusion

The paper stresses the high incidence of intracranial infection when a complete occipital dermal sinus and dermoid cyst are present. Two case reports are presented and analyzed, in addition to 17 reported cases in the literature during the past 10 years. Important clinical and radiological findings are given.

Staphylococcus aureus is the main source of bacterial infection, causing meningitis, cerebellar abscess, and infection of the dermoid cyst. Because infection of the dermoid cyst or central nervous system makes surgery more difficult and hazardous, diagnosis of this condition should be made before infection occurs.

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The Use of Radioactive Rose Bengal in the Evaluation of Infantile Jaundice

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Although the ideas concerning neonatal and infantile jaundice have changed considerably in the past two decades, there still remain several serious voids in the understanding of the pathogenesis of this disease group and in the ability to make a reasonably accurate premortem diagnosis.

Diagnostic inadequacy is most evident in differentiating between (1) those diseases resulting in complete and relatively permanent biliary obstruction and (2) those diseases resulting in various degrees of biliary obstruction but with a reasonable probability that, at some phase of the disease, the biliary tree will be patent and functioning.

The disease groups to be differentiated would include intra- and extrahepatic biliary atresia; bile duct stenosis, lithiasis, tumor, cyst; annular pancreas, etc., versus the various forms of hepatitis, inspissated bile syndrome, and possibly some diseases or pathological states as yet unidentified; plus some instances or phases of bile duct stenosis, lithiasis, tumor, and cyst.

The following criteria have been utilized with varying degrees of accuracy regarding the differential diagnoses of complete from incomplete biliary obstruction in infants.

1. The conventional liver chemistries—fair to poor.[1-5]

2. Obtaining serial bilirubin determinations—fair.[2,4,6-8]

3. Exploratory laparotomy—fair to good, with some important contraindications.[2,4,9-14]

4. Operative cholangiogram.[9,15]

5. Biopsy and biopsy interpretations—poor to good.[4,7,16-21]

6. Specificity of giant-cell transformation—controversial.[1,5,10,15,22-25]

7. The use of sulfobromophthalein (Bromsulphalein; BSP) as a liver function test. This has been of little value in this group of liver diseases.[4,26,27] Duodenal intubation combined with a BSP test has been of value only under experimental conditions in animals or in similar situations in human beings with T-tubes in the bile duct, following biliary tract surgery.[28-30] Attempts to recover small amounts of sulfobromophthalein from the duodenum in almost complete obstruction is unreliable, owing to the difficulty of measuring low levels of the dye and the possibility of not obtaining the proper sample via the duodenal tube.[15,28,30] Although all these studies have added to our knowledge of liver physiology, they have not been quantitative enough to be of aid in solving the problem posed in this report. The use of intraduodenal magnesium sulfate has been suggested as a diagnostic and therapeutic test for the cases of inspissated bile syndrome.[31]

8. Clinical observation—poor to good.[32,33]

There are varying degrees of optimism and pessimism among investigators with regard to the over-all prognosis of infants with prolonged obstructive jaundice, and this has altered their various diagnostic approaches. Gellis,[12] Weech,[32] Swenson (5%),[33] and Gerrish et al.[34] feel that the number of operable lesions is quite small. On the other hand, 16% to 34% were thought to be helped by operation by Holmes,[35] Kieswetter et al. (16%),[4] Moore (26%),[36] Myers et al. (22%),[14] and Gross (34%).[37] Except for Gross and Kieswetter, the latter authors included only cases of extrahepatic biliary atresia, which fact accounts for the higher incidence of operable lesions. Gross and Kieswetter, however, did include patients with hepatitis, and they therefore disagree with Gellis, Gerrish, and Weech with regard to over-all prognosis.

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Actually, even this discrepancy can be resolved if one examines Gross's data carefully. His impression is that hepatitis "is much less common than the biliary obstructions in the same age group. It can generally be recognized by abnormalities in one of several tests, as the cephalin flocculation test, the sulfobromophthalein retention test, a reduced prothrombin level of the serum, or a lowered serum protein. In addition, the child appears to be more ill than is generally the case with biliary obstruction and the stools are seldom acholic." [37]

In Gross's series of 198 cases, 35 surgical improvements were recorded in cases which supposedly had inspissated mucus plugs in the extrahepatic ducts. Many of these could have been cases of hepatitis which cleared after surgery. This seems plausible, since his criteria for diagnosing "hepatitis" in the newborn would eliminate many cases which other authors would include as "hepatitis," namely, some patients with normal liver chemistries and acholic stools. In any event, the discrepancy between those investigators who report success following operation or a high incidence of operable lesions versus those who are pessimistic rests not only with case selection in any series, but also reflects the various interpretations of the same diagnostic data.

The importance of an early diagnosis has been commented upon by many authors.[1,4,12,14,15,32,34-38] Craig and Landing reported, "Since biliary atresia may give rise to irreparable damage to the liver within two and one-half months of birth, early examination and, if necessary, exploration with liver biopsy appears to be indicated in any case of prolonged neonatal jaundice in which the diagnosis is not made clear by other means." [1]

On the other hand, Gellis stated, ". . . the number of children with atresia of the bile ducts amenable to surgery is small and infants with obstructive jaundice due to conditions other than atresia of the bile ducts tolerate surgery poorly. For these reasons, it is wise to delay surgery until it is certain from studies conducted on the infant and from the course of the illness that the obstruction is not clearing." [12]

These views are not incompatible, for one is emphasizing good management in cases of atresia and the other proper management of infantile hepatitis. Both views rather reflect the poor diagnostic armamentarium at hand, which necessitates generalizations.

Materials and Methods

A preliminary report of this test was previously published, including its methodology in abstract form.[39]

Thirteen infants with the onset of jaundice before the age of 2 months were included in this study. Liver function and biliary metabolism were periodically evaluated with the conventional chemical procedures. In addition, punch biopsy of the liver was performed with a Vim-Silverman needle in those cases in which biliary atresia was the most likely diagnosis. Some of the patients had a second biopsy several weeks later.

Radioactive rose bengal,* 1μc. to 4μc. was injected intravenously into all the patients. One

* Abbott Laboratories.

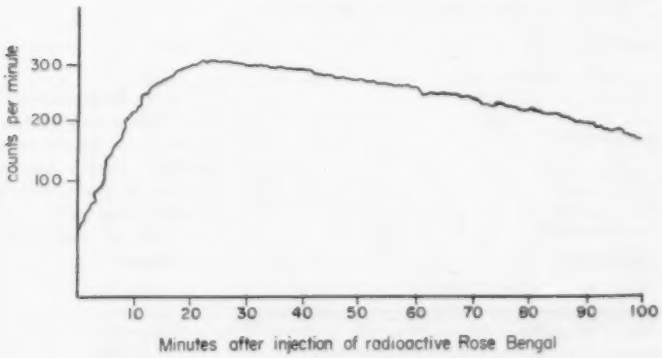

Fig. 1.—Normal liver function, as demonstrated by the uptake and excretion of radioactive rose bengal.

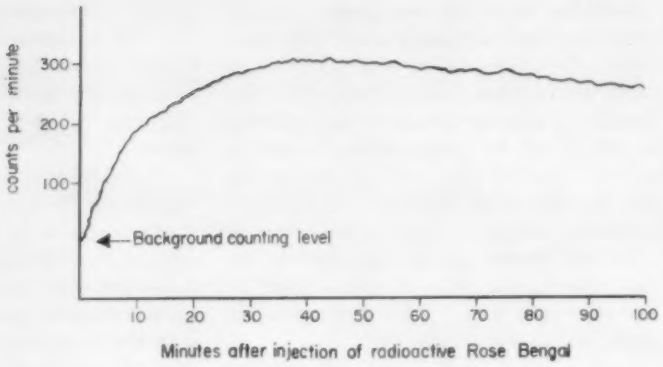

Fig. 2.—Radioactive uptake curve as measured by a superficial counter over the liver. Mild hepatitis, as demonstrated by a slow uptake and a relatively normal excretory rate of radioactive rose bengal.

microcurie was found to be sufficient and was used in most of the patients. Twenty-four-hour urine and stool specimens were collected over a period of three to six days. The 24-hour stool collections were emulsified in twice normal sodium hydroxide at 60 C for one hour. Two milliliter aliquots of both urine and emulsified stool were counted in a well-type scintillation counter. From these values the daily excretion of radioactivity in the urine and feces was determined.

Superficial counting over the liver region was accomplished with external counting equipment. The slopes of uptake and excretion of rose bengal were obtained (Figs. 1-4).

Results

The superficial scanning of the liver following the administration of radioactive rose bengal has been found useful in adults.[41-44] Consistent observations have been reported from qualitative statistical scanning (hepatoscan) and from quantitative uptakes.[42] The fact that a considerable dose can be directed to the thyroid in adults with severe obstructive jaundice was reported recently, thus adding a slight hazard to the large doses used in the hepatoscans.[40] The data obtained in infants were inconsistent. The resulting graphs exhibit the liver uptake and excretion curves of a normal infant (Fig. 1); an infant with mild "hepatitis" (Fig. 2); an infant with severe "hepatitis" (Fig. 3), and an infant with intrahepatic biliary atresia (Fig. 4). Only very gross variations can be detected by this method. It is very difficult to separate the severe obstructive phase of "hepatitis" from true intrahepatic biliary atresia, since the excretory phase of the curve in both conditions is nearly flat (Figs. 3 and 4). Furthermore, (1) the dose administered in performing a superficial scan has to be relatively large; (2) because of the infant's small size the counting equipment cannot avoid counting some radioactivity in the duodenum, gallbladder, and heart; (3) the

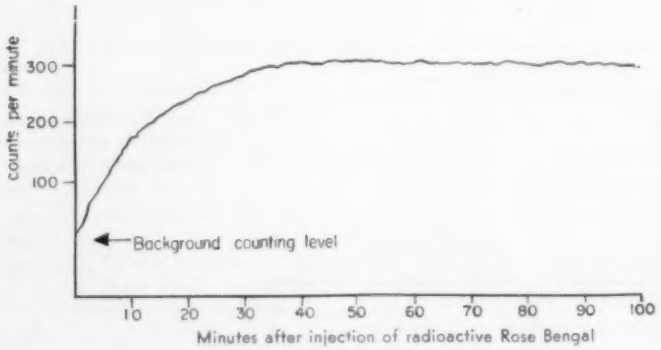

Fig. 3.—Radioactive uptake curve as measured by a superficial counter over the liver. Severe hepatic injury, as demonstrated by both a slow uptake and excretion of radioactive rose bengal.

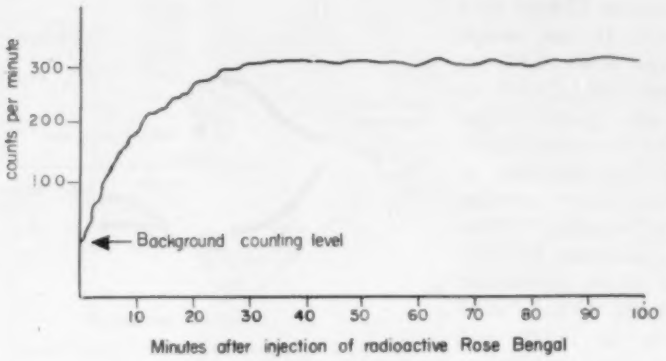

Fig. 4.—Intrahepatic biliary atresia as demonstrated by a reduction in the excretory rate of radioactive rose bengal. The shape of this curve cannot be easily differentiated from the curve in Figure 3, and therefore in itself is of little diagnostic value.

infant has to be immobilized for several hours, and (4) slight movement of either the infant or the counter can completely invalidate the results. Therefore, this method has been of little help in the differentiation of infantile hepatobiliary disease.

On the other hand, the radioactivity in the urine and feces yielded some interesting results.

Excretion of Rose Bengal in the Stool.

In no instance would one expect to find absence of radioactivity in the stool, since some free I^{131} is present in the rose bengal even before administration. Furthermore, it has been shown that I^{131} is released from the rose bengal while it is in the liver.[45] Since iodide can diffuse throughout the body, one would expect some radioactivity in the stool even with complete biliary obstruction. This was the case; and in four proved cases of biliary atresia the total 72-hour stool content of radioactivity, corrected for decay, contained approximately 2% of the administered radioactivity (Table, Cases 6, 7, 8, and 9).

Three other patients were suspected of having biliary atresia clinically, due to a rising bilirubin, persistent bilirubinuria, clay-white stools and, relatively normal liver chemistries (Table, Cases 3, 4, and 5). In fact, Case 5 had a liver biopsy diagnosed as intrahepatic biliary atresia. The 72-hour content of radioactivity in the stool was 51.8%, 4.4%, and 24.8% of the administered radioactivity in Cases 3, 4, and 5 respectively (Table).

One month later Patients 4 and 5 had repeat determinations which demonstrated

The Excretion of Radioactivity After the Intravenous Administration of Rose Bengal in Patients with Infantile Jaundice

Patient	Age	Per Cent Administered Radioactivity			Biopsy Diagnosis	Final Diagnosis
		72 Hr. Stool	24 Hr. Urine	72 Hr. Urine		
1	4 days	27.2	0.3	1.9	--	Erythroblastosis
2	5 days	33.3	7.9	11.8	--	Physiologic jaundice
3	3 mo.	51.8	2.6	5.5	--	"Hepatitis" *
4	3 mo.	4.4	--	--	Giant cell hepatitis	"Hepatitis"
	4 mo.	17.2	3.1	7.1		
5	4 mo.	24.8	--	--	Biliary atresia	"Hepatitis"
	5 mo.	36.2	--	--	"Hepatitis"	
6	7 mo.	2.4	--	--	Biliary atresia	Biliary atresia
7	6 mo.	1.9	11.6	23.0	Biliary atresia	Biliary atresia
8	6 mo.	1.9	6.1	12.7	--	Biliary atresia
9	6 mo.	2.1	--	19.0	Giant cell transformation	Biliary atresia

* The term "hepatitis" in this discussion refers to the syndrome of prolonged infantile jaundice with eventual clearing or residual liver damage, which may be due to viral hepatitis, inspissated bile syndrome, hepatitis of undermined etiology, and other liver diseases as yet undefined.

an increase over the previous 72-hour stool content of radioactivity. In one month Patient 4 had readings from 4.4% to 17.2%. Patient 5 went from 24.8% to 36.2% excretion in one month's time (Table). At the time of the second determination, the jaundice was beginning to clear, and a second liver biopsy specimen was considered to show "hepatitis." There was no question on the initial test in Cases 3 and 5, that complete biliary obstruction was not present, with the 72-hour stool content of radioactivity at 51.8% and 24.8%, at the time that biliary atresia was the tentative diagnosis. The 4.4% excretion in Case 4 demonstrated the sensitivity of this test in predicting incomplete obstruction when all other clinical and laboratory tests indicated complete obstruction; thus the rose bengal test contradicted the original diagnosis, and eventually Cases 3, 4, and 5 turned out not to be biliary atresia.

Cases 1 and 2 and four other patients (not in Table) with elevated bilirubin levels indicated that even in hemolytic hepatobiliary diseases with a high bilirubin level, the stool content of radioactivity was well above the range where complete obstruction would be considered.

Excretion of Radioactivity in the Urine. It is well known that rose bengal does not pass through the gastrointestinal epithelium or the kidney glomeruli and tubule epithelium in any significant amounts, and, in fact, is "picked up" from the vascular compartment only by the liver and thence excreted into the biliary and gastrointestinal tract, never to be reabsorbed (Fig. 5).[42,44,45]

Therefore, one would never expect to find any appreciable radioactivity in the urine. But it has been reported that radioactivity does appear in the urine of rats and that this radioactivity was the result of free I^{131}, detached from the rose bengal molecule.[45] These workers also showed that the iodide dissociation occurs in the liver. Thus, the longer rose bengal remained in the liver the greater was the amount of iodide released for kidney excretion and thyroid uptake.

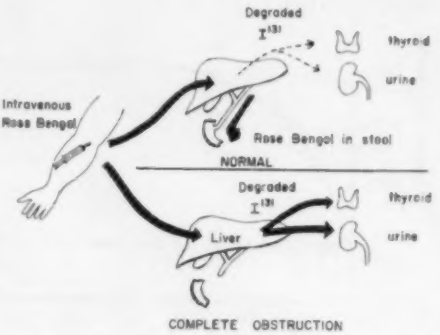

Fig. 5.—The excretion of radioactivity in normal and obstructed patients following the intravenous administration of radioactive rose bengal. The normal excretion of radioactive rose bengal is via the liver, bile ducts, and gastrointestinal tract. In cases of biliary obstruction the liver dissociates the iodide from the rose bengal, allowing it to be accumulated by the thyroid or excreted in the urine.

If these data could be carried over from rat to man, one would expect that the longer the rose bengal remained in the liver, provided the parenchymal liver cells could still degrade the rose bengal, the greater the amount of iodide released. If this were true, patients with true biliary atresia should degrade the largest amount of rose bengal, since there is complete physiological obstruction and relatively normal functioning liver cells (Fig. 5). Conversely, patients with unobstructed biliary ducts and normal liver parenchyma would degrade the least amount of iodide from any given dose of rose bengal.

The Table lists both the 24-hour and 72-hour urine content of radioactivity. It can be observed that the patients with biliary atresia had a higher percentage of administered radioactivity in the urine than did the patients with patent biliary passages. It is difficult to analyze the data since the number of cases one can see with the symptoms under investigation is too small to permit adequate statistical evaluation. Furthermore, urine analysis was not started at the initiation of the project, so all the possible cases were not studied from this viewpoint.

Figure 6 contains the excretion curves for one case of biliary atresia (M. S.) ver-

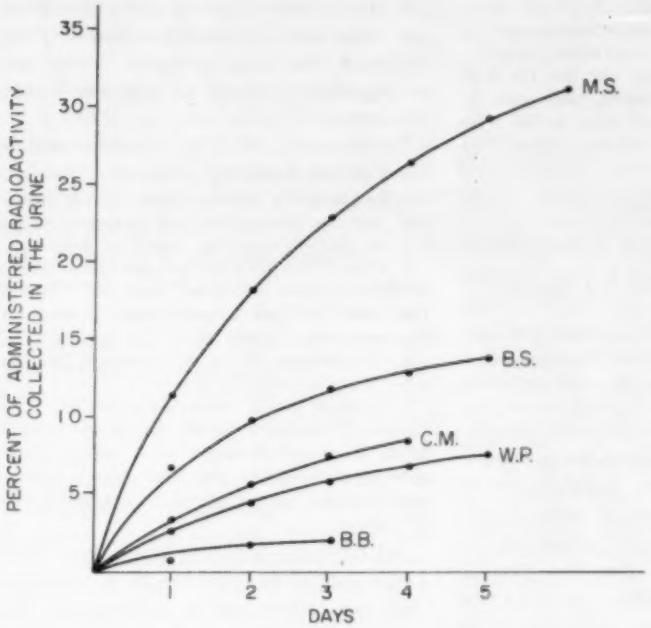

Fig. 6.—After the administration of radioactive rose bengal free iodide may appear in the urine. All patients but M. S. had an unobstructed biliary tree and excreted in their urine low levels of radioactive iodine. M. S. (biliary atresia) excreted considerably larger amounts of the radioactive iodine in his urine.

sus five other jaundiced patients without biliary atresia. The case of biliary atresia (M. S.) excreted the largest amount of radioactivity (I^{131}) in the urine. Whether or not the excretion curve is diagnostic of biliary atresia will be discussed later.

The urinary excretion curve can be altered by one other factor, namely, the variability of the patient's thyroid function. As further evidence that the iodide is degraded, Patient M. S. had 7.9% of the administered radioactivity in his thyroid one week after the original injection of rose bengal. This is further proof that iodide is released from the rose bengal molecule in vivo. Therefore, the magnitude of the urinary excretion of radioactivity will vary inversely with the radioiodine uptake of the thyroid and directly with the turnover rate of the thyroid.

At the present time we can conclude that some cases of biliary atresia may be diagnosed by an elevated urine excretion alone, but the infallibility of this method needs further evaluation.

Comment

Stool Excretion Test.—The rose bengal excretion test offers many advantages over previous tests of biliary patency. Its ease of performance and more quantitative results make the diagnosis of complete biliary obstruction relatively easy. The excretion of 2% or less of the administered radioactivity in the stool is strong evidence for complete obstruction. Not enough cases have been analyzed for one to know the variation in the stool content in complete obstruction or the highest stool content that can exist in the presence of complete obstruction. One can point to Case 4 (Table) as evidence of the stool content in incomplete obstruction, namely, 4.4%. This would seem to indicate that the maximum stool radioactivity consistent with the diagnosis is somewhere between 2% and 4%. The advantages and disadvantages of the *stool excretion determination* are as follows:

Advantages

1. It offers the most positive evidence for biliary patency.

2. It is a quantitative test.
3. The technical procedure is relatively easy.
4. The dose of radiation is extremely small.
5. The better the prognosis, the less the dose of radiation to viable tissue, since most of the radioactive decay will occur in the fecal material or outside of the body, rather than the liver.

Disadvantages

1. A radioisotope laboratory or its equivalent must be accessible.
2. Separation of the urine and feces is essential.
3. No case has yet needed more than a 72-hour stool collection for correct diagnosis, but it is conceivable to miss the stool containing radioactivity in a case of severe constipation.

In cases of neonatal or infantile jaundice where biliary atresia is seriously considered, *the stool excretion can definitely prove biliary patency* even when all other clinical and laboratory data support atresia as the initial diagnosis. This was the case in Patients 3, 4, and 5 (Table). In this event neither laparotomy nor Vim-Silverman needle biopsy is necessary, and the avoidance of these procedures is an added benefit of this test. The test is more accurate than liver biopsy at the present time, and less dangerous.

On the other hand, we have no concept of the range of stool radioactivity content in cases of hepatitis during the severe obstructive phase. All the cases in this series with 2% of the administered radioactivity in the stool proved to be biliary atresia. Conceivably, this could occur with the severest cases of hepatitis.

Thus, while this test can definitely rule out biliary atresia, it can only indicate complete biliary obstruction until we know whether cases of "hepatitis" can or cannot yield as low as 2% stool radioactivity, and what percentage of "hepatitis" cases would fall into this category.

Urine Excretion Test.—The urine excretion results are being reported not because they offer a test of biliary patency better than or equal to the stool excretion test but because this test may be able to yield valuable information about the excretory function of the liver. There is still a possibility that when sufficient cases are carefully investigated, the urine excretion curve may be diagnostic in cases of complete biliary obstruction.

Theoretically, the urine excretion test is based on the following premises:

1. Rose bengal is rapidly excreted by the normal liver into the biliary tract and duodenum, where it is not reabsorbed in any significant amounts.
2. While in the liver a small percentage of the radioactive iodide is released from the molecule. The longer the rose bengal remains in the liver the more iodide is released.
3. The released I^{131} is then excreted into the urine or taken up by the thyroid.
4. In biliary atresia one would expect to see the highest I^{131} release, since the rose bengal remains in the liver until it decays or is degraded, and, since in early atresia the liver parenchyma has good function, one might predict a reasonably high I^{131} release.

All the cases of biliary atresia tested had a high content of radioactivity in the urine. Only one infant had a simultaneous estimate of thyroid radioactivity, and therefore the total release of I^{131} is not known in most of the cases. Thus, this test could prove to be diagnostic with just a 24-hour urine test along with the oral strong iodine solution, U.S.P. (Lugol's solution).

In this small series, no case of extrahepatic complete biliary obstruction was encountered (such as extrahepatic bile duct atresia, stenosis, cyst, etc.). It is in the differentiation of these cases that the urinary excretion test may be most helpful, for release of iodide may occur only if rose bengal is retained in the liver parenchyma, while if it can fill the extrahepatic biliary tree, little or no iodide may be released. Thus, it may be possible to differentiate extrahepatic biliary atresia from intrahepatic biliary atresia, since the former may have both a low content of I^{131} in the urine and a low stool excretion test, while intrahepatic atresia has a high content of I^{131} in the urine and a low stool excretion test.

Liver Biopsy.—This was not a study of the value of liver biopsy in the management of the jaundiced infant. At the present time

its value is controversial, and the results depend on the laboratory reporting the data.[4,7,15-22] Many do agree that giant-cell transformation is not specific and that errors can be made with the aid of the punch biopsy technique.[1,3,13,15,22-25] If one utilizes a laparotomy biopsy procedure in a case of "hepatitis," a definite risk is being taken with the patient's survival.[3,4,8-14]

The question of whether intrahepatic biliary atresia is really viral hepatitis which has occurred in utero or early in the neonatal period has been raised by some authors and not accepted by others.[38,46] There is definite evidence that the biliary tree is still developing in the neonatal period.[4,24,47] If "hepatitis" can produce forms of liver disease which resemble biliary atresia in the neonatal period, then it is possible that the radioactive rose bengal stool excretion test, performed before complete obstruction has occurred, might document quantitatively the development of a case of intrahepatic "biliary atresia."

The congenital nature of "viral hepatitis" infection, as well as the familial occurrence of the disease, has been adequately stressed by others.† Biliary atresia has also occurred in families, and one wonders about the possible association mentioned in the previous paragraph.[57,58] Most cases of atresia have been presented as case reports without a family history.[7,14,20,59-62] Lastly, several cases of unrelated congenital malformations have occurred in children born to mothers with known infectious or serum hepatitis.[63-66] The majority of such pregnancies result in either a normal infant or, rarely, one with liver disease.[11,21,63,64,67,68]

It is important to mention this fact, for the possible teratogenic effect of maternal hepatitis should not be confused with the fetal liver involvements late in pregnancy. One may describe the latter as pathological, rather than teratological to avoid the controversy present in the literature.

Needless to say, the present status of this group of diseases is still unclear, owing partly to its complex nature and partly to the rarity of cases on any one pediatric service.

† References 1, 11, 24, 25, 49-52, 54-56.

Summary

The term "hepatitis" in this discussion refers to the syndrome of prolonged infantile jaundice with eventual clearing or residual liver damage, which may be due to viral hepatitis, inspissated bile syndrome, hepatitis of undetermined etiology, and other liver diseases as yet undefined.

A test using low doses of radioactive rose bengal is introduced for the purpose of evaluating infantile jaundice. The technique, advantages, and disadvantages are presented.

The stool excretion technique proved to be of great value in differentiating cases of severe biliary obstruction, as in "hepatitis," from complete biliary obstruction, as in intrahepatic biliary atresia. Excretion of approximately 2% of the administered radioactivity was consistent with the diagnosis of complete obstruction. Patients who were thought to have complete obstruction excreted amounts which automatically ruled out complete obstruction, although the clinical, laboratory, and biopsy findings had pointed to the diagnosis.

The stool excretion test can eliminate the necessity for biopsy in certain cases of "hepatitis" that mimic biliary atresia and also eliminate the delay in making the diagnosis which is necessary if serial bilirubin determinations are to be relied upon. Furthermore, the urgent necessity of surgical exploration can be eliminated if the biliary tract is demonstrated to be present.

The theory of the urine excretion test using rose bengal is presented, and the possibility is offered that it may aid in the differential diagnosis between extrahepatic and intrahepatic biliary obstruction, since the rose bengal may not be degraded in the biliary tract as well as in the liver. This would mean that different amounts of I^{131} would appear in the urine although complete biliary obstruction was present in both types. Furthermore, this test may reveal a

great deal about the nature of the excretory function of the liver. It may enable us to delineate aspects of neonatal liver function.

There was a definite increase in the urine radioactivity in cases of complete obstruction. The exact value of this phase of the test has to be examined with more cases.

The superficial counting technique for the evaluation of liver uptake and excretion gave inconsistent results in infants. The liver biopsy gave erroneous results, but no condemnation of this procedure can fairly be made by the evidence presented, since liver biopsy evaluation was not the purpose of this study and the procedure may be more useful in other hands.

The suggestion that intrahepatic biliary atresia may be the result of intrauterine or neonatal hepatitis is cited. The possibility that the stool excretion portion of the rose bengal test may be able to document quantitatively the development of a case of intrahepatic biliary atresia is presented. The validity of this thesis is neither accepted nor denied.

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Infantile Nephrosis

Clinical, Biochemical, and Morphologic Studies of the Syndrome

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The nephrotic syndrome occurs infrequently prior to the second year of life. When nephrosis does develop during the first year, the course differs from that of older children with nephrosis, being characterized by an extremely poor prognosis and an almost complete refractoriness to therapy. Despite its low incidence, infantile nephrosis is important, not only because of the severity of the disorder itself but also because the occurrence of nephrosis in this age group raises questions regarding the etiology of the disease.

Since 1952, we have studied 12 patients who developed nephrosis during the first year of life. These cases illustrate the characteristic clinical and laboratory features of the disease, the difficulties in management, and the inordinately high mortality rate of infantile nephrosis. The purpose of this paper is to present a clinical and laboratory analysis of these cases, together with morphologic observations obtained by kidney biopsy and autopsy material, studied by light and electron microscopy.

Materials and Methods

Kidney tissue was obtained by either percutaneous needle biopsy or open surgical biopsy, as has been described previously.[1,2] The tissue was processed for both light and electron microscopy by methods which have been previously described.[2,3] Frozen and alcohol-fixed tissue was prepared for examination with the polarized microscope to search for crystals, as described by Giles et al.[4] Microdissection was carried out using the procedure described by Oliver.[5]

Report of Cases

Tables 1-4 present data pertaining to each case and should be consulted when reading the case reports.

Table 1.	Clinical Course
Table 2.	Laboratory Findings
Table 3.	Response to Treatment
Table 4.	Pathologic Findings

CASE 1.—This 6 lb. 3 oz. (2,805 gm.) female infant was born of a normal delivery and seemed normal for the first two days of life. The child's mother had had moderate peripheral edema and minimal hypertension during the later months of pregnancy. At 2 days of age the baby developed circumoral cyanosis which was improved by oxygen therapy, and the infant was discharged in good condition at 7 days of age. The child's mother first noted periorbital edema at the time of discharge from the hospital, and distinct periorbital edema was apparent by 4 weeks of age. The infant was admitted to a hospital, and the following abnormal laboratory results were obtained: 4+ albuminuria, hypoalbuminemia (0.6 gm. %), and elevation of the serum cholesterol (207 mg. %). Peripheral edema was first noted at 5 weeks of age, at which time her weight had increased to 9½ lb. (4,310 gm.).

She was transferred to the University of Minnesota Hospitals at the age of 7 weeks. The family history revealed that a previous male child had had nephrosis and had died with uremia at 14 months of age; however, an autopsy was not performed. A paternal aunt had died of renal failure at 33 years of age, and one of the aunt's daughters had had acute glomerulonephritis.

Physical examination revealed a very edematous infant who was cyanotic while crying. The abdo-

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Fig. 1 (Case 1).—Infant at 7 weeks of age, showing generalized edema.

men was very distended by fluid, and 4+ pitting edema of the extremities and sacrum was found. Systolic blood pressure in the arm was 110 mm. Hg. The anterior fontanelle was very large. Figure 1 shows this patient at 7 weeks of age.

The hemoglobin was 11.4 gm. %, and white blood cells numbered 11,500/cubic millimeter, with 44% polymorphonuclear leukocytes. The erythrocyte sedimentation rate (ESR) was 86 mm. per hour (Westergren), blood urea nitrogen (BUN) 13 mg. %, serum albumin 0.3 gm. %, serum globulin 2.1 gm. %, and serum cholesterol 218 mg. %. Urinalysis revealed 3+ albumin and very occasional granular casts. A urine culture was negative. X-rays of the chest were normal, and x-rays of the skull showed only widely open suture lines. An intravenous pyelogram showed prompt excretion of dye, but adequate visualization of the upper urinary tract was not obtained. A biopsy of the right kidney was obtained at surgery. Microscopic sections of the biopsy specimen showed striking tubular dilatation and distention of Bowman's spaces. Most of the glomeruli were normal, although some small, incompletely developed glomeruli were present. In addition some glomeruli showed hypercellularity and minimal basement membrane thickening.

Corticotropin gel (ACTH gel) was administered in a dose of 36 mg. daily, supplemented by potassium chloride, tetracycline, and an antacid (Maalox). Corticotropin was continued at the original dosage level for 14 days, when diuresis began, and then gradually decreased over the next 10 days. Although the diuresis resulted in a decrease of 1,200 gm. in body weight, there was little change in the degree of proteinuria and no change in the serum protein level. Following the corticotropin treatment, leukocytes appeared in the urine, and repeated urine cultures grew out Escherichia coli which were sensitive only to chloramphenicol (Chloromycetin). A disturbance of blood electrolytes, characterized by acidosis, hyperchloremia, and azotemia, developed, which persisted until her death at 5 months of age.

The gross autopsy findings were ascites, periorbital edema, hemorrhagic bronchopneumonia of the right upper and right middle lobes, and large pale kidneys. Microscopically, the kidneys showed the same changes noted in the biopsy specimen (Fig. 2).

Case 2.—This male infant was born of an uncomplicated pregnancy and weighed 6 lb. (2,720 gm.). He seemed "tremulous" for one week after birth, but was otherwise well until 19 days of age, when transient swelling of his feet was noted. Edema of his face, extremities, and trunk developed at one month of age. He was admitted to a hospital where he received five transfusions over a three-week period. Temporary relief from edema followed each transfusion. He was also noted to have bouts of cyanosis, and cardiac enlargement was demonstrated by x-ray.

The family history was noncontributory in that his mother and father and a 5-year-old sibling were well.

He was admitted to the University of Minnesota Hospitals at 3 months of age. Physical examination revealed a pale, edematous infant weighing 4,700 gm. Numerous scattered telangiectases were observed. Systolic blood pressure was 110 mm. Hg in the arms and 150 mm. Hg in the legs. The liver edge was at the level of the umbilicus, and the spleen tip was 2 cm. below the left costal margin. An umbilical hernia and large bilateral inguinal hernias were present.

Urinalysis revealed 2+ protein and 1+ erythrocytes. The hemoglobin was 8.2 gm. %, ESR 138 mm. per hour, BUN 22 mg. %, serum albumin 0.5 gm. %, serum globulin 2.4 gm. %, and serum cholesterol 278 mg. %. An intravenous pyelogram was normal. A 12-hour urine specimen contained 380 mg. of protein, 720,000,000 leukocytes, 76,000,000 erythrocytes, and 4,300,000 casts. The urea clearance was 60 cc/minute (corrected to 1.73/sq. m. body surface area).

He was treated with mechlorethamine (nitrogen mustard) 0.2 mg/kg. on two successive days, and his body weight fell to 2,900 gm. in the subsequent

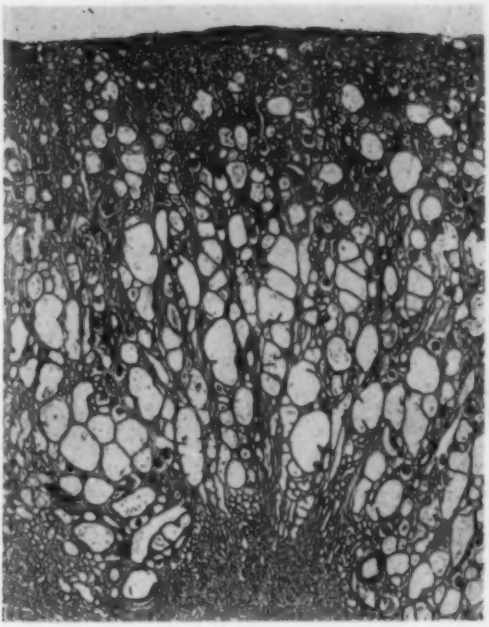

Fig. 2 (Case 1).—Kidney showing marked cystic dilatation of the cortical tubules and dilatation of Bowman's spaces; ×7.

10 days. There was no change in the degree of proteinuria or hematuria during the diuresis, and the serum protein level did not change significantly. A second course of nitrogen mustard one month later had no beneficial effect, and 20 mg. of corticotropin daily for nine days produced no improvement. Two weeks later he was given a 16-day course of cortisone at a dosage of 70 mg.

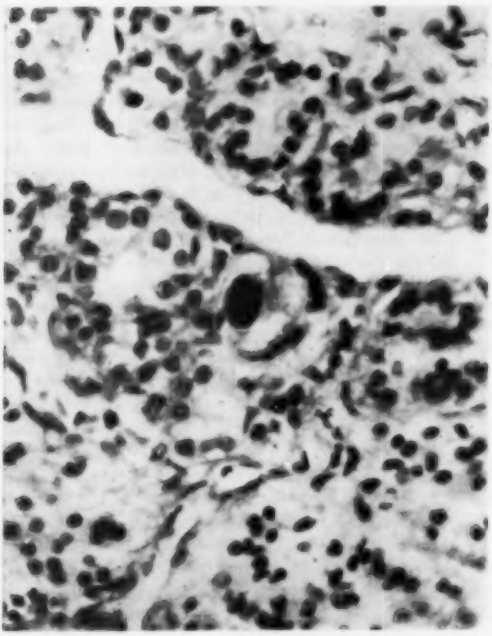

Fig. 3 (Case 2).—Submaxillary gland, showing a cytomegalic inclusion; ×450.

Fig. 4 (Case 2).—Kidney, showing moderate diffuse dilatation of the cortical tubules and Bowman's spaces; × 7.

per day. He became dehydrated, developed diarrhea and oliguria, and died three months after admission.

An autopsy revealed pneumonia and swollen pale kidneys. Microscopic study of the lungs, pituitary, submaxillary glands, and pancreas showed basophilic intracellular inclusion bodies, compatible with cytomegalic inclusion disease (Fig. 3). Examination of the kidneys showed marked tubular dilatation, glomerular hypercellularity, occasional hyalinized glomeruli, thickening of the glomerular capsule, and a moderate degree of interstitial inflammatory reaction (Fig. 4).

Case 3.—This female infant was born of a pregnancy complicated by pyelonephritis in the second trimester. She weighed 6 lb. (2,720 gm.) at birth, and her immediate neonatal course was not unusual. A urinalysis obtained on the fifth day of life (reason for the procedure not established) revealed 4+ albumin, 2+ sugar, and 2+ red blood cells. Periorbital edema appeared at about 10 days of age, and the infant was referred to the University of Minnesota Hospitals.

It was learned that two previous children born to these parents had died in infancy. The first child died shortly after birth and no cause was determined. The second child died at 17 days of age and was found at autopsy to have an interventricular septal defect. The family history was otherwise negative.

Physical examination revealed a pale, edematous infant with circumoral cyanosis and a mottled cyanotic discoloration over the lower abdomen. Firm masses, thought to be the kidneys, were easily palpated in each flank. The balance of the examination was negative.

The hemoglobin was 16.5 gm. %, and the white blood cell count was 11,200, with 80% polymorphonuclear leukocytes. Urinalysis showed 2+ albumin, 2+ sugar, 2+ red blood cells, and 2+ coarse granular casts. The ESR was 91 mm. per hour. Serum albumin was 0.6 gm. %, and serum globulin 2.5 gm. %. The serum cholesterol was 240 mg. %, BUN 14 mg. %, and blood glucose 65 mg. %. A Wassermann test was negative. X-rays of the heart and chest were negative. An electrocardiogram was normal. An intravenous pyelogram was unsatisfactory, and a right retrograde pyelogram revealed questionable elongation of the renal calyces. A small wedge of renal cortex was obtained at surgery. Microscopic study of this tissue showed striking dilatation of the renal tubules and distention of Bowman's spaces, with relatively normal glomerular structure. Numerous eosinophilic casts were noted in the distal nephron (Fig. 5).

The patient was treated with corticotropin gel in a dose of 15 mg. twice daily. Potassium chloride, an antacid, and tetracycline were given concurrently. A weight loss of 400 gm., thought to represent a diuresis of edema, was noted on the

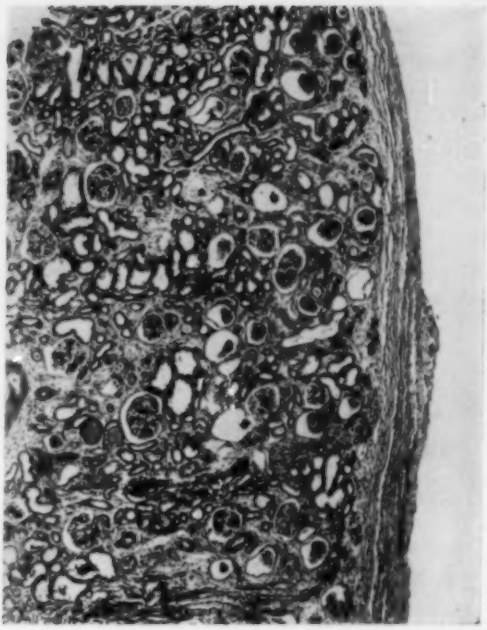

Fig. 5 (Case 3).—Renal biopsy, showing dilatation of cortical tubules and Bowman's spaces; × 50.

14th day of hormone therapy. However, on the 15th day of treatment the patient suddenly seemed worse, refused to eat, and became cyanotic. A wound abscess beneath the renal biopsy site was drained. Peritoneal aspiration revealed cloudy fluid, which contained numerous E. coli bacteria. The patient died later that day.

Gross autopsy revealed perforation of multiple gastric and duodenal ulcerations, peritonitis, and a paranephritis abscess. Microscopic examination of the kidneys revealed striking dilatation of the proximal tubules and Bowman's spaces. The epithelium of the dilated tubules was very flat, and numerous eosinophilic tubular casts were observed. Although some of the glomeruli were small and hypercellular, the majority of glomeruli were thought to be normal by light microscopy.

Case 4.—This female infant was born of a normal pregnancy and delivery, and weighed 5 lb. 1½ oz. (2,310 gm.). Although periorbital edema was noted on the sixth day of life, the infant was thought to be well until 3 weeks of age, when she was seen by the family physician for refusal to take formula. Periorbital and pitting edema of the extremities was present at that time. Urinalysis revealed 4+ albumin and negative tests for sugar and acetone. The serum albumin was 1.04 gm. %, and the serum globulin 2.51 gm. %.

At the time of admission to the University of Minnesota Hospitals, it was learned that the only other child in the family was in good health. The paternal grandfather and the child's father were said to be "allergic" to various tree pollens.

Physical examination revealed a pale infant with intermittent blotchy cyanosis of the skin and generalized edema and ascites. Her weight was 2,730 gm. Systolic blood pressure was 95 mm. Hg in the arms and 105 mm. Hg in the legs. A Grade 2 systolic murmur was heard at the base of the heart, and the right kidney was thought to be enlarged to palpation.

The hemoglobin was 12.9 gm. %, and the white blood cell count was 12,750, with 52% polymorphonuclear leukocytes and 5% eosinophils. Urinalysis revealed 1+ albumin, occasional red and white blood cells, and fine granular casts. The ESR was 128 mm. per hour, BUN 14 mg. %, serum albumin 0.3 gm. %, serum globulin 2.2 gm. %, and serum cholesterol 295 mg. %. A 12-hour urine specimen contained 32,000 casts; 2,800,000 white blood cells, 362,000 red blood cells, and 270 mg. of protein. X-rays of the chest, cardiac fluoroscopy, and an electrocardiogram were normal. An intravenous pyelogram revealed normal anatomy and normal excretion of the dye.

During the patient's hospital course, a gradual increase in edema and weight was noted, despite a rather poor food intake. She died unexpectedly on the seventh day in the hospital.

Gross autopsy findings included generalized edema and ascites, pulmonary congestion and edema, a small hemorrhage in the left temporal

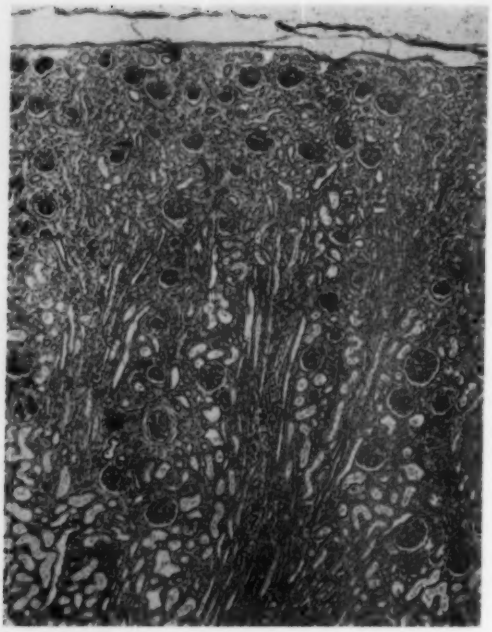

Fig. 6 (Case 4).—Kidney, showing moderate hypercellularity and hyalinization of a few glomeruli near the pyramid; × 50.

region of the brain, and brownish material, presumed to be old blood, over the base of the brain. The kidneys were grossly normal and weighed 45 gm. each. Microscopic pathologic examination of sections of the lungs, spleen, pancreas, heart, adrenals, striated muscle, stomach, liver, small intestine, and uterus revealed no abnormalities. A specific search for inclusion bodies was made and none was found. The kidney tubules were normal except for moderate dilatation of some proximal tubules and the presence of considerable albuminous material in the distal nephron. Most of the glomeruli were normal. An occasional glomerulus near the pyramid showed partial hyalinization, but the degree and distribution of the change were not considered to be a definitive pathologic finding (Fig. 6).

Microscopic sections of the brain showed scattered old and new hemorrhages in the subarachnoid and intraventricular spaces and within the cerebral cortex.

CASE 5.—This female infant was born six weeks prematurely and weighed 4 lb. 12 oz. (2,155 gm.). Abdominal swelling and frequent cyanotic spells occurred during the first weeks of life. The abdominal swelling increased, and by 7 weeks of age, generalized edema and ascites were present. Five hundred milliliters of ascitic fluid was removed by paracentesis prior to her transfer to the University of Minnesota Hospitals.

Family history was negative in that both parents were well, and there were no siblings.

Physical examination revealed a small female infant with short extremities, marked edema, and ascites. The liver was moderately enlarged, and the tip of the spleen was palpable.

The initial urinalysis showed 2+ albumin and normal sediment. Examination of the blood revealed hemoglobin 10.7 gm. % and normal leukocyte and differential cell counts. The serum albumin was 0.4 gm. %, serum globulins 1.8 gm. %, serum cholesterol 326 mg. %, and BUN 12 mg. %. A 12-hour urine specimen contained 0.44 gm. of protein, 81,000,000 erythrocytes, and 2,300,000 leukocytes. The serum calcium was 3.9 mg. % and the serum inorganic phosphorus 10.6 mg. %. Both of these values returned nearly to normal after parathyroid hormone administration.

The patient was given repeated serum albumin infusions, without demonstrable improvement. Repeated convulsions, which failed to respond to calcium gluconate injections, occurred following a blood transfusion.

The edema spontaneously disappeared six weeks after admission, but there was little change in the laboratory findings. She developed diarrhea and moderate dehydration, and died two months after admission.

An autopsy revealed moderate atelectasis of the lungs, hypercellularity and minimal basement membrane thickening of the renal glomeruli. Bow-

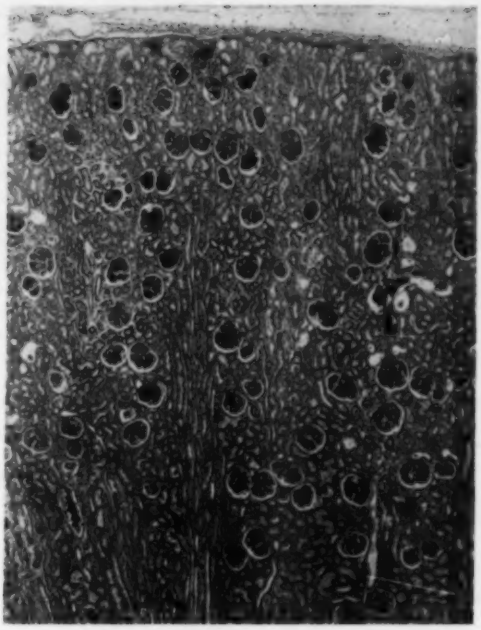

Fig. 7 (Case 5).—Kidney, showing moderate hypercellularity of glomeruli and a few eosinophilic casts; × 50.

man's capsule was moderately distended around a few glomeruli. The tubules contained occasional eosinophilic casts, but were otherwise not remarkable (Fig. 7).

CASE 6.—This patient was reported previously as an example of familial nephrosis (Case 4, Ref. 6). Since three other children in this family had developed nephrosis, the mother of this child was carefully observed during her fourth pregnancy and was found to develop toxemia during the last trimester. The delivery was normal, and the placenta was normal. Urine from this infant was examined immediately after birth and was found to contain 2+ protein. Although serum protein and cholesterol levels of cord blood were normal, hypoproteinemia and hypercholesterolemia developed within the first month of life. Edema appeared at one month of age and has been present continuously in the subsequent four years of observation. Treatment has consisted of a 12-day course of corticotropin, a 15-day course of cortisone, and a 7-month trial of cortisone therapy on 3 consecutive days of each week. No significant improvement has been noted during the observation of this child, and she continues to demonstrate all the clinical findings and the serum and urine abnormalities of the nephrotic syndrome.

Renal biopsies were performed at 3 months and 3 years of age. Light microscopic examination of the biopsy specimens revealed no abnormalities.

CASE 7.—This male infant was noted to have edema of the periorbital tissues, feet, and legs at the age of 3 months. He was first studied at a large medical center at the age of 4 months, where a diagnosis of nephrosis was established. Recurrent severe infections, including two attacks of peritonitis, occurred over the subsequent four years. The generalized edema which had developed by 6 months of age varied from time to time, but moderate proteinuria was constantly present.

A sibling had "congenital nephrosis" and died with uremia at the age of 4½ years. The mother had moderately severe toxemia during the third trimester of both pregnancies.

He was admitted to the University of Minnesota Hospitals at 4 years of age. Physical examination revealed moderate generalized pitting edema and ascites. Blood pressure was 114/70 mm. Hg. A left inguinal hernia was noted. The balance of the examination was normal.

The BUN was 12 mg. %, ESR 98 mm. per hour, serum albumin 0.7 gm. %, serum globulin 2.8 gm. %, and serum cholesterol 500 mg. %. Routine urinalysis showed 2+ protein, and a 12-hour urine specimen contained 9,000,000 red blood cells, 68,000 casts, and 180 mg. of protein. The antistreptolysin-O titer was less than 50 units per milliliter. An intravenous pyelogram was normal.

A renal biopsy was obtained by the needle biopsy technique. Light microscopic study of the tissue revealed normal renal morphology.

The patient was treated with oral cortisone in a dose of 200 mg. per day for a period of 27 days. There was no decrease in edema, and no change in the abnormal laboratory values. During the interval in which the cortisone dosage was being decreased, the patient developed severe hypertension, convulsions, and coma. He recovered completely within about 10 days.

Follow-up studies have failed to reveal any significant change in the degree of edema or proteinuria over the past two years.

CASE 8.—This patient has been previously reported as an example of familial nephrosis (Case 1, Ref. 6). Edema was noted at four months of age and was continuously present throughout the remainder of his life. Hypertension was first noted at the age of 2½ years. He was hospitalized five times prior to his first admission to the University of Minnesota Hospitals at 6 years of age. Physical examination revealed generalized edema, a blood pressure of 130/100 mm. Hg, and retinal vascular ischemia. Serum albumin was 0.7 gm. %, cholesterol 474 mg. %, and ESR 115 mm. per hour. A 12-hour urine specimen contained 3 gm. of albumin and more than 1,000,000,000 red blood cells. There was little change in his course during five additional hospital admissions, despite therapy which included one 17-day course of ACTH and five courses of nitrogen mustard. During his final admission, his hypertension was controlled by reserpine and hydralazine hydrochloride therapy, and another course of corticotropin was begun. However, after six days this treatment was discontinued, when his blood pressure rose to 160/120 mm. Hg and uremia developed. The uremia increased progressively until his death one month later. Light microscopic examination of kidney tissue, obtained by biopsy two months prior to death, showed the histologic appearance of chronic glomerulonephritis. Essentially the same renal pathologic findings were present at autopsy.

CASE 9.—This patient has been reported previously as an example of familial nephrosis (Case 3, Ref. 6). Albuminuria and microscopic hematuria were found at 4 months of age, and she became edematous a short time later. She has been observed for 5½ years and has always shown edema, hypertension, and the characteristic laboratory findings of the nephrotic syndrome. She has received two courses of corticotropin, one course of cortisone, and two courses of nitrogen mustard, without improvement. Two kidney biopsies have shown changes consistent with subacute glomerulonephritis when studied by light microscopy.

CASE 10.—This female infant was well until the age of 7 months, when she developed periorbital edema following a mild upper respiratory illness. Generalized edema and ascites developed during the subsequent three weeks, and she was admitted to the University of Minnesota Hospitals on Nov. 6, 1956.

A history of hay fever and eczema in the mother's family was obtained. A sibling had died of intestinal obstruction, and no renal abnormalities were detected at autopsy.

Physical examination revealed generalized edema and ascites. Her blood pressure was 105/70 mm. Hg.

The hemoglobin was 11.6 gm. %, and the white blood cell count was 10,900. Urinalysis showed 4+ protein and 1+ red blood cells. The ESR was 93 mm. per hour, BUN 10 mg. %, serum albumin 0.4 gm. %, serum globulin 3.3 gm. %, and serum cholesterol 618 mg. %. Electrophoretically, the plasma albumin was 0.4 gm. %, α_1-globulin 0.1 gm. %, α_2- and β-globulins 3.8 gm. %, and γ-globulin 0.4 %. An intravenous pyelogram was negative.

Microscopic study of a surgical biopsy of the right kidney showed minimal glomerular hypercellularity, but was otherwise normal.

Daily intramuscular injections of 60 mg. of corticotropin were administered for 14 days beginning Dec. 13, 1956. A decrease in edema, loss of 600 gm. of body weight, disappearance of albuminuria, and a return of serum protein levels toward normal occurred by the 10th day of therapy. Studies obtained at the end of the course of corticotropin therapy revealed: normal urinalysis, serum albumin 3.0 gm. %, serum globulin 3.0 gm. %, serum cholesterol 139 mg. %, and ESR 23 mm. per hour.

During the interval of treatment with corticotropin, it was learned that a bichloride of mercury solution had been used as a rinse for the infant's diapers for a period of three weeks from about Aug. 20, 1956, through Sept. 3, 1956. A 24-hour urine specimen, which was collected in a mercury-free container on Dec. 21, 1956, was found to contain 27μg. of mercury. A second 24-hour urine specimen, collected on Dec. 31, 1956, contained 18μg. of mercury.*

She is apparently entirely well 24 months after onset of the disease.

We interpret this as a possible case of mercury-induced nephrosis in an infant.

CASE 11.—This case has been previously reported (Case 22, Ref. 2). He was an 8-month-old

* We are indebted to Mr. G. J. Raschka of the Industrial Health Laboratories of the Minnesota State Board of Health for these determinations. Urine from normal children does not contain mercury in quantities detectable by the method used in this study.[7]

infant who developed progressive edema without a preceding illness. He was admitted to the University of Minnesota Hospitals three weeks later, at which time severe edema and moderate hypertension were found. His urine contained 3+ albumin and occasional red blood cells. The BUN was 100 mg. %, CO_2 10 mEq. per liter, and serum potassium 6.0 mEq. per liter. Serum albumin was 0.7 gm. % and total serum cholesterol was 434 mg. %. He was treated with nitrogen mustard, without improvement. Renal insufficiency progressed, and he died at 10 months of age. A renal biopsy three weeks before death and the autopsy both demonstrated severe glomerular alterations consistent with the pathologic diagnosis of chronic glomerulonephritis.

CASE 12.—This male infant was born of a normal pregnancy and delivery. His mother, father, and two older siblings were well. He was well until 10 months of age, when he developed swelling of the feet and eyelids, and rapid weight gain. He was hospitalized at 11 months of age, and a diagnosis of nephrosis was established. Treatment with corticotropin and a low-salt diet for 10 days resulted in a weight loss of 2 lb., but the laboratory abnormalities remained unchanged.

The diagnosis of nephrotic syndrome was confirmed in another hospital at one year of age, and he was treated with cortisone for one month and was then given intravenous nitrogen mustard and intravenous albumin. A transient weight loss occurred, but the laboratory findings did not improve. Another course of albumin and nitrogen mustard therapy one month later produced a 2 kg. weight loss, but again, no change in the laboratory abnormalities.

He was admitted to the University of Minnesota Hospitals at 14 months of age. Physical examination revealed generalized edema. His blood pressure was 110/70 mm. Hg. Laboratory findings included: 2+ proteinuria and 2+ red blood cells in the urine sediment. The sedimentation rate was 110 mm. per hour, BUN 15 mg. %, serum albumin 0.7 gm. %, serum globulin 4.2 gm. %, and serum cholesterol 998 mg. %. A 12-hour urine specimen contained 112,000,000 red blood cells, 1,000,000 white blood cells, 800,000 casts, and 0.62 gm. of protein.

Examination of kidney tissue obtained by needle biopsy revealed hypercellularity, lobulation, and partial hyalinization of most of the glomeruli. A few epithelial crescents were seen, and a few glomeruli were almost completely hyalinized (Fig. 8).

He was treated with corticotropin-zinc for 16 days. His laboratory findings remained unchanged, and his weight increased 3½ lb. He was then treated with cortisone for 18 days and was then given nitrogen mustard over a three-day period. During the cortisone therapy, he developed vomiting and diarrhea, and these symptoms became worse after the cessation of cortisone. He became

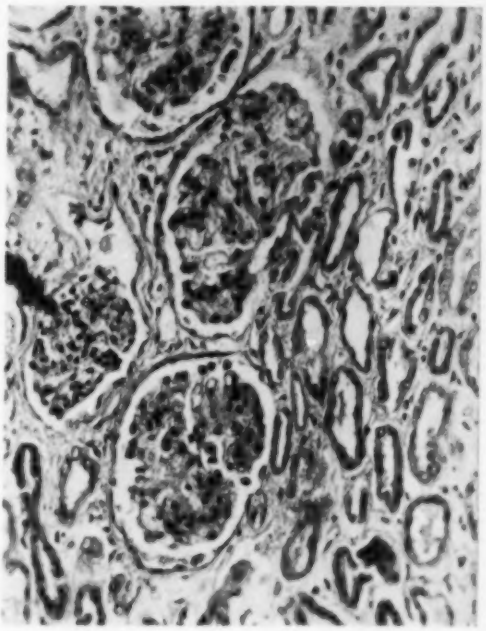

Fig. 8 (Case 12).—Kidney, showing lobulation, thickened basement membranes, and capillary occlusion in the glomeruli; × 250.

dehydrated, developed pneumonia and septicemia, and died two and one-half months after admission.

Aside from edema, the only gross autopsy findings were enlargement and pallor of the liver and both kidneys. Microscopic examination of the kidneys revealed essentially the same pathology as that described for the renal biopsy which was obtained three months prior to death.

Clinical Summary

A review of the preceding case reports reveals several unusual features which distinguish infantile nephrosis from the nephrotic syndrome as it usually occurs in older children. These features are the early age of onset, the resistance to therapy, the poor prognosis, and the higher familial incidence.

Six of the twelve patients developed the nephrotic syndrome within one month after birth. Edema was the presenting symptom in all six patients, although albuminuria was detected in two patients prior to overt edema (Table 1).

The other six patients became edematous between 3 and 10 months after birth. Suggestive evidence of mercury intoxication was present in one patient, and the mercury was considered to be a possible cause of the nephrosis. In one patient, cytomegalic inclusion body disease was found at autopsy.

One patient had evidence of renal failure when first seen; the other eleven patients appeared initially to have uncomplicated or "pure" nephrosis. All of the patients had the characteristic findings of the nephrotic syndrome: edema, albuminuria, hypoalbuminemia, hypercholesterolemia, and elevation of the erythrocyte sedimentation rate (Table 2). Microscopic hematuria was detected in at least one urine specimen from every patient.

The serum cholesterol was lower in the patients whose disease began in the neonatal period than in those whose disease became manifest at a later age. However, since the cholesterol is normally lower during the neonatal period, the elevation above the normal for that age is probably as significant

TABLE 1.—*Clinical Course of Infantile Nephrosis*

Case No.	Age of Onset of Edema	Sex	Comments
1	1 wk.	F	Older brother with infantile nephrosis; mother had toxemia
2	19 days	M	Family history negative; one normal sibling
3	10 days	F	Albuminuria at 5 days of age; two sibs died in infancy (unrelated causes)
4	6 days	F	Family history negative; one sibling well
5	Birth	F	Hypocalcemia (3.9 mg. %) responded to parathormone; spontaneous diuresis without laboratory improvement
6	1 mo.	F	Albuminuria at birth
7	3 mo.	M	Older siblings with "congenital" nephrosis; mother had toxemia with both pregnancies
8	4 mo.	M	Sibling of Case 6
9	4 mo.	F	Sibling of Case 6
10	8 mo.	F	$HgCl_2$ diaper rinse up to one week prior to onset
11	8 mo.	M	Uremia when first seen; rapid progression
12	10 mo.	M	Family history negative; two normal siblings

TABLE 2.—*Laboratory Findings in Infantile Nephrosis*

Case No.	BUN	Albumin	Globulin	Cholesterol	ESR	Addis - 12 Hours		
						Protein (Grams)	RBC (Millions)	Casts (Millions)
1	13	0.6	1.9	218	86	(3+)	—	0
2	22	0.5	2.4	278	138	0.38	76	4.3
3	—	0.6	2.5	240	91	(2+)	(2+)	(2+)
4	14	0.3	2.2	295	128	0.27	0.302	0.032
5	12	0.4	1.8	326	56	0.44	81	—
6	13	0.8	2.5	281-536	112	0.9	37	—
7	12	0.7	2.8	500	98	0.18	9	0.068
8	10	0.7	3.1	500	115	3	1,400	0.5
9	10	0.9	2.7	677	131	2.5	20	0.9
10	10	0.4	3.3	618	93	(2+)	(1+)	—
11	100	0.7	2.6	434	133	0.06	38	0.25
12	15	0.7	4.2	998	110	0.62	112	0.8

as the striking elevations seen in the older children.

Therapy was almost universally unsuccessful in these patients. One patient died before treatment could be started. Another was treated only symptomatically, with a low-salt diet and intravenous albumin. The other 10 patients received the usual forms of therapy for nephrosis. These included 10 courses of corticotropin, 4 courses of cortisone, 11 courses of nitrogen mustard, and 2 courses of cortisone and nitrogen mustard combined (Table 3).

TABLE 3.—*Response to Treatment in Infantile Nephrosis*

Case No.	Type of Treatment	Response
1	Corticotropin gel—150 mg/sq. m/day for 14 days	Diuresis; no change in proteinuria or blood chemistries
2	1. Nitrogen mustard—0.4 mg/Kg.	Diuresis; no improvement in urine or blood chemistries
	2. Nitrogen mustard—0.4 mg/Kg.	No effect
	3. Corticotropin—100 mg/sq. m/day for 9 days	No effect
	4. Cortisone—350 mg/sq. m/day for 16 days	Diuresis without improvement in laboratory findings; died a few days later with dehydration and oliguria
3	Corticotropin gel—150 mg/sq. m/ day for 14 days	Moderate diuresis on 14th day; no change in urine; died the next day of perforated ulcer
4	None	None
5	1. Albumin and blood intravenously	None
	2. None	Spontaneous diuresis without laboratory improvement; died one week later with dehydration
6	1. Corticotropin—150 mg/sq. m/day for 12 days	None
	2. Cortisone—300 mg/sq. m/day for 15 days	None (hypertension)
7	Cortisone—300 mg/sq. m/day for 27 days	None (hypertension, convulsions and coma)
8	1. Nitrogen mustard—0.4 mg/Kg., 5 courses at intervals	None
	2. Corticotropin—150 mg/sq. m/day for 6 days	None (hypertension, uremia, death)
9	1. Corticotropin—150 mg/sq. m/day for 10 days	None
	2. Corticotropin—150 mg/sq. m/day for 17 days	None
	3. Cortisone—300 mg/sq. m/day for 17 days	None
	4. Nitrogen mustard—0.4 mg/Kg., 2 courses	None
10	Corticotropin—150 mg/sq. m/day for 14 days	Diuresis with complete remission
11	Nitrogen mustard—0.4 mg/Kg.	None
12	1. Corticotropin—zinc—70 mg/sq. m/day for 16 days	None
	2. Cortisone—300 mg/sq. m/day for 19 days, followed by nitrogen mustard—0.4 mg/Kg.	None; died a few days later of sepsis

With one exception, none of these treatments produced a remission. Three patients had a diuresis, but neither these three nor the other patients showed improvement in the laboratory abnormalities. In addition, one patient had a spontaneous diuresis, and even this spontaneous diuresis was not accompanied by improvement in the urine and serum findings.

The one exception to these discouraging results was the patient with possible mercury nephrosis (Case 10) who had a diuresis with a disappearance of all the laboratory abnormalities following withdrawal from the exposure to mercury plus a course of corticotropin. This remission has lasted for two years without further therapy.

The deaths of three patients seemed directly related to therapy. One patient died of a perforated ulcer following corticotropin therapy; another died of an overwhelming sepsis following combined cortisone-nitrogen mustard therapy, and the third died of hypertension and progressive uremia which developed a week after corticotropin was begun.

A poor prognosis has paralleled the poor response to therapy. Eight of the twelve patients have already died, and three have active, resistant disease. Only the patient with possible mercury nephrosis appears to have recovered, and even in this patient, the duration of the remission is too short to allow an unequivocally good prognosis to be given. The causes of death were diverse. Two patients died of renal insufficiency; three died of infection; one died of intracranial hemorrhage, and two apparently died from fluid and electrolyte imbalances.

The incidence of familial nephrosis in this group is 5 out of 12 patients, or 42%. Three of the ten families from which these

TABLE 4.—*Pathologic Findings in Infantile Nephrosis*

Case No.	Age at Biopsy or Autopsy	Source of Tissue	Pathologic Findings	
			Light Microscopy	Electron Microscopy
1	2 mo.	Biopsy	Marked dilatation of proximal tubules and Bowman's spaces; glomeruli normal	Diffuse loss of epithelial cell foot processes
	6 mo.	Autopsy	Same findings	None
2	6 mo.	Autopsy	Dilatation of proximal tubules; moderate hypercellularity of glomeruli; cytomegalic inclusion body disease	None
3	4 wk.	Biopsy	Dilatation of proximal tubules; hypercellular glomeruli	Diffuse loss of epithelial cell foot processes
	8 wk.	Autopsy	Same as above	None
4	1 mo.	Autopsy	Normal kidneys	None
5	4 mo.	Autopsy	Hypercellular glomeruli; basement membranes slightly thickened; arterioles thickened	None
6	3 mo.	Biopsy	Normal kidney	Diffuse loss of epithelial cell foot processes
	3 yr.	Biopsy	Normal kidney	None
7	4 yr.	Biopsy	Normal kidney	Diffuse loss of epithelial cell foot processes; endothelial hypercellularity
8	7 yr.	Biopsy	Chronic glomerulonephritis	Variable loss of foot processes of epithelial cells; severe endothelial cell proliferation and great increase in basement membrane-like material; lamina densa irregularly thickened
	7 yr.	Autopsy	Chronic glomerulonephritis	None
9	27 mo.	Biopsy	Subacute glomerulonephritis	Diffuse loss of epithelial cell foot processes; nodular thickening of lamina densa
	3½ yr.	Biopsy	Subacute glomerulonephritis	None
10	10 mo.	Biopsy	Normal kidney	Diffuse loss of epithelial cell foot processes
11	9½ mo.	Biopsy	Chronic glomerulonephritis	Variable loss of foot processes of epithelial cells. Severe endothelial cell proliferation and great increase in basement membrane-like material; lamina densa irregularly thickened
	10 mo.	Autopsy	Chronic glomerulonephritis	None
12	14 mo.	Biopsy	Subacute glomerulonephritis	Diffuse loss of epithelial cell foot processes; nodular thickening of lamina densa
	16 mo.	Autopsy	Subacute glomerulonephritis	None

cases arise had two or more children with infantile nephrosis.

Pathological Findings

The renal pathology of the infant nephrotics varied over as wide a range as that of the older children with nephrosis.[2] In this series, two groups of patients could be defined on the basis of the pathological findings. The first group comprises nine patients with changes similar to those observed in childhood nephrosis. The microscopic findings varied from "no renal lesion" through proliferative glomerulonephritis to severe chronic glomerulonephritis. Five patients (Cases 4, 5, 6, 7, and 10) had essentially normal glomerular morphology; two (Cases 9 and 12) showed the changes of subacute proliferative glomerulonephritis; and two (Cases 8 and 11) had definite chronic glomerulonephritis.

The second group consists of three patients (Cases 1, 2, and 3) in whom the outstanding finding was a marked dilatation of the proximal convoluted tubules without evident change in the rest of the tubules. The glomeruli in these cases showed minimal proliferative and membranous changes, but the degree of change was not sufficient to suggest postglomerular ischemia as the cause of the tubular dilatation. No obstruction of the tubules could be demonstrated, either on the routine sections or in the dissected nephron; thus the cause of the tubular dilatation remains unknown.

Electron Microscopic Studies

Electron microscopic studies were carried out in nine of the patients. The findings in

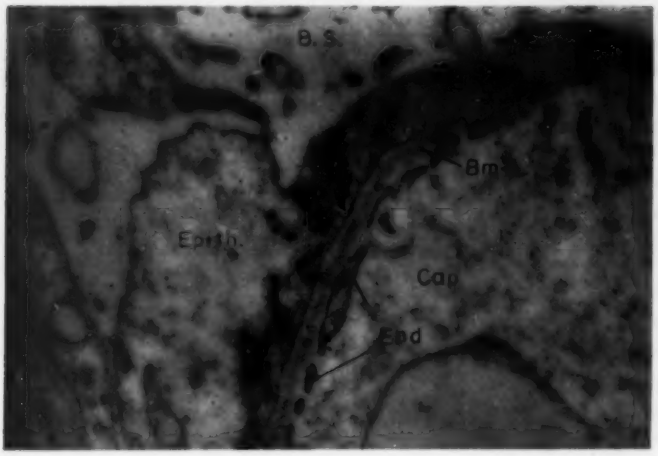

Fig. 9 (Case 3).—Electron micrograph of a section of a glomerular capillary. Note the total absence of epithelial cell foot processes (arrows). The basement membrane and endothelium are normal; reduced about 28% from mag. × 60,000. *B. S.*, Bowman's space. *Epith*, epithelium. *Bm*, basement membrane. *End*, endothelium. *Cap*, capillary lumen.

Cases 6, 8, and 9 have been reported previously.[8] The glomerular changes in the other patients were similar, showing loss of the epithelial cell foot processes and smudging of the epithelial cytoplasm along the lamina densa (Fig. 9). These changes are identical with those shown by older patients with the nephrotic syndrome. An additional abnormality was present in biopsy specimens from Cases 8, 9, 11, and 12, consisting of an increase in the number of endothelial cells, nodular thickening of the basement membrane, and an accumulation of basement membrane-like material in the glomerular tuft (Fig. 10). Of greatest interest are the findings in Patients 1 and 2, both of whom had the severe tubular dilatation with little evident glomerular abnormality under the light microscope. Both of these patients demonstrated the typical foot process changes of the epithelial cell which are characteristic of the nephrotic syndrome. Therefore, even though the tubular changes dominate the light microscopic appearance in these patients, it seems evident that the glomerular lesion is the same as that occurring when tubular changes are minimal.

Spiro[9] has recently presented observations on the neonatal glomerulus which indicate that foot processes are not fully developed until later in life. This finding might suggest that the glomerular mor-

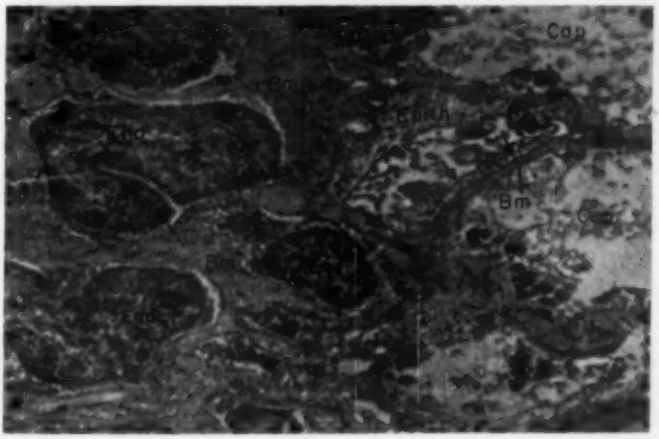

Fig. 10 (Case 12).—Electron micrograph of a section from a typical glomerulus. On the left, the capillary spaces are obliterated by endothelial hypercellularity and by excess basement membrane-like material. On the right, the open capillaries show a typical foot process abnormality (arrows); however, the endothelium is also abnormal; reduced about 34% from mag. × 8,500. *End*, endothelium. *Bm*, basement membrane. *Epith*, epithelium. *Cap*, capillary lumen.

phology of nephrotic infants does not differ from that of normal infants. However, our observations of renal morphology by electron microscopy in normal infants and newborn animals indicate that foot processes are present at birth.[10] We would conclude, therefore, that the smudging of the foot processes in infantile nephrosis is a pathologic change which has the same relation to the nephrotic syndrome as does the foot process lesion in childhood nephrosis.

Special Studies

The gross tubular organization was investigated by microdissection of the kidneys of Case 1, in which the most striking degree of dilatation was observed in the routine microscopic sections. The length of the tubules appeared approximately normal for the patient's age. The distal three-fourths of the proximal tubule was enlarged, varying from 3 or 4 to 50 times the normal diameter. The tremendous cystic areas seen on the routine section were identified as localized dilatations near the distal end of the proximal tubules. The tubular wall was extremely thin, appearing almost transparent under the dissecting microscope. The portion of the tubule leading to this cystic area was enlarged and quite opaque in appearance, suggesting that this area was hypertrophied rather than dilated.

The first portion of the proximal convoluted tubule and the entire tubule distal to the thin limb appeared normal. No constriction could be identified to suggest obstruction as the cause of the dilatation.

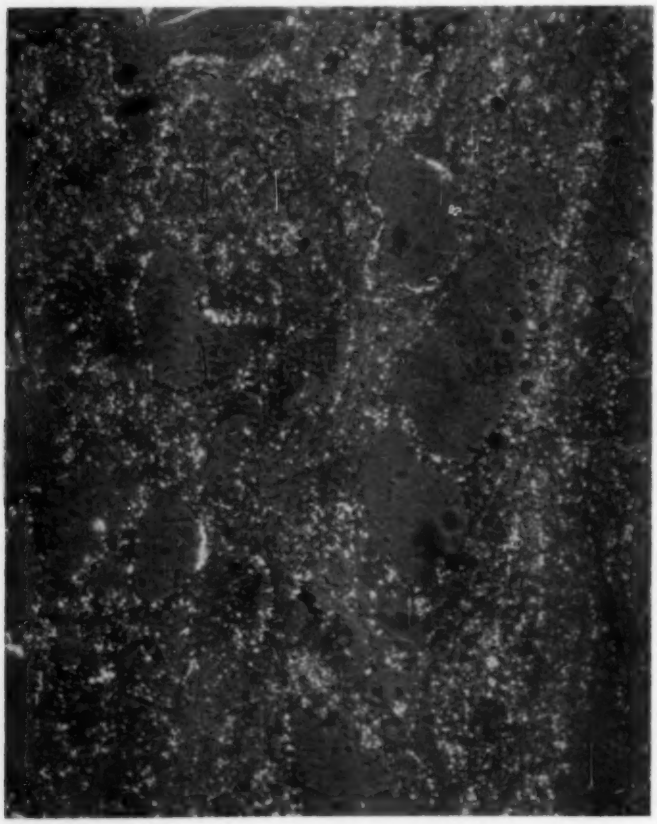

Fig. 11 (Case 1).—Unstained alcohol-fixed kidney, photographed with partial polarization. Numerous crystals are present which appear to occupy nearly every cell; × 100.

A search for crystals was made in Case 1 by examining alcohol-fixed sections, both stained and unstained, with polarized light. Large numbers of crystals were found in the liver, kidney, spleen, and lymph nodes (Fig. 11). However, no crystals were found in sections of frozen unfixed tissue, and control tissue fixed in alcohol and examined with polarized light showed the same crystals as those seen in the tissues of the patient. It therefore appears that the crystals did not preexist, but were produced artificially by the alcohol fixation, probably as a result of crystallization of protein by the alcohol.

An attempt was made to determine whether the mother of Cases 6, 8, and 9 had circulating antibodies against human kidney, using the Coons fluorescent antibody technique. Blood was drawn from the mother one month and six months after the birth of Case 6. γ-Globulin was separated from the serum, labeled with fluorescein isocyanate, and applied to frozen sections of kidney from Case 6 and to normal infant's kidney. No specific localization of the γ-globulin could be demonstrated.*

Comment

In addition to the early onset, the most striking characteristics of infantile nephrosis are refractoriness to treatment and a poor prognosis. These features have been characteristic of all cases thus far reported.[4,11-16] Among the patients with neonatal nephrosis described since adrenal steroid therapy has been in use, none has survived and only one has lived beyond one year. In the present series, only the patient who developed nephrosis after the administration of mercury appears to have a favorable outlook. Thus, it would seem that present methods of treating nephrosis are inadequate to control the infantile form, and that either more effective nonspecific therapy, or a more specific approach must be developed before the prognosis will improve. The extremely grave prognosis of the infants with nephrosis is in marked contrast to the relatively good prognosis of older children treated with adrenal steroid therapy, in whom the survival rate is estimated to be between 70% and 80%.[17]

Another feature of infantile nephrosis which differs from those characteristic of idiopathic childhood nephrosis is its high familial incidence. Fanconi et al.[13] and Giles et al.[4] have reported familial cases of infantile nephrosis, and a high familial incidence was observed in the present series. The familial occurrence of nephrosis, in the absence of cases in consecutive generations, suggests that in some infants either the nephrosis itself, or the predisposition to the development of nephrosis, may be inherited as a recessive characteristic. The consanguinity in the cases reported by Giles et al.[4] supports this hypothesis. Although the precise familial incidence of childhood nephrosis is unknown, it is certainly much lower than that of the infantile form.

No definite evidence is available at present to indicate whether or not the etiology of infantile nephrosis is the same as that of idiopathic childhood nephrosis. The much higher familial occurrence, the greater severity, and the unusual tubular pathology[4,12,15] of infantile nephrosis suggest that the etiology may be different from the etiology of nephrosis in older patients. On the other hand, the similarity of the submicroscopic lesion of the glomerular epithelial cell foot processes might suggest that the etiology is the same. The observed differences might be explained by a severer effect of the same disease process upon the immature kidneys of infants. The high incidence of prematurity noted by others[11,14,18] may be significant in this connection.

The most widely accepted theory regarding the etiology of human nephrosis proposes that the renal damage results from an autoimmune process in which the patient produces antibody directed against his own kidneys. The evidence offered in support of this hypothesis is indirect,[18-20] and,

*We are indebted to Dr. Albert Coons of the Harvard Medical School for carrying out these determinations.

even though no satisfactory alternative has been offered, this hypothesis must remain in question until more proof is available. Certainly it seems unlikely that an immune reaction is the cause of nephrosis in the infant, since, as pointed out by Gruskay and Turano,[16] the immunologic unresponsiveness which features the first weeks of life[21] should not permit the development of a sufficient antibody response on the part of the newborn to produce an immunological disease. Further, the presence of established nephrosis in some infants a few hours after birth indicates that insufficient time has elapsed to permit an antibody response, even if the infant were capable of responding immunologically.

One way to reconcile the occurrence of nephrosis in a neonate with the autoimmune theory is to assume that the disease might begin in utero as a consequence of an immune response by the mother. Antibodies produced by the mother might be directed against antigens in the fetal kidney, the maternal kidney, or even the placenta. Such a mechanism could also explain infantile nephrosis without requiring immunological participation on the part of the baby. This possibility is supported by the observation that the mothers of all the patients with familial nephrosis in our series had toxemia with each pregnancy. This circumstance suggests that the kidneys of both the mother and the fetus might be damaged by some mechanism which leads to reversible disease in the mother and irreversible nephrosis in the baby. However, toxemia has not been noted in either the familial cases of nephrosis reported by others or the nonfamilial neonatal cases reported in this series. If toxemia were etiologically important, it would be necessary to postulate a different pathogenic mechanism for those infants whose mothers have experienced a normal pregnancy, unless one postulates that a maternal factor might injure the fetal kidney without producing clinical disease in the mother.

In addition, the apparently delayed onset (as long as 10 months after birth) in some cases of infantile nephrosis would be difficult to explain on the basis of antibodies transferred to the baby from the mother. It is also difficult to explain the progressive nature of the nephrosis in these infants by implicating antibodies passively transferred to the baby prior to birth, even though it has been shown[22] that nephrotoxic serum nephrosis, a disease presumably based on passively transferred antibody, may become a persistent disease in rats, and the similarities between this experimental model and the suggested mechanism involving the mother are obvious.

Our attempts to demonstrate the existence of maternal antibodies directed against fetal kidney were unsuccessful. However, this does not eliminate the possibility that maternal antibodies may be responsible for nephrosis in some infants.

Several other factors have been implicated as possible causes of infantile nephrosis, either from our own studies or from the findings of others.

One child (Case 10) was exposed to mercury prior to the onset of nephrosis, and the mercury seemed to be implicated as an inciting cause of the nephrosis. Since the role of mercury as a cause of the nephrotic syndrome seems well established,[13] we had no reason to question its importance in our infantile patient. Withdrawal of mercury and concomitant treatment with corticotropin resulted in the apparent recovery of this infant. Although it is not possible to assess the separate roles of these two circumstances in this child, her complete recovery is in contrast with the poor outcome in all other cases of infantile nephrosis, and we feel that her course is consistent with the diagnosis of nephrosis due to mercury.

In another patient (Case 3) of this series, the characteristic morphologic abnormalities of cytomegalic inclusion disease were found at autopsy. Giles et al.,[4] who also found cytomegalic inclusion disease in one of their patients with infantile nephrosis, considered the occurrence of the two diseases to be coincidental. However, the finding of an additional patient in whom the two diseases

coexisted raises the possibility that some unidentified relationship may exist between the two diseases.

Since cytomegalic inclusion disease is relatively common in infants, and since the kidney is frequently involved in cytomegalic inclusion disease without producing a nephrotic syndrome,[23] it seems likely that the occurrence in our case is also coincidental. However, the possibility must be considered that an occasional case of the nephrotic syndrome may represent another of the many manifestations of cytomegalic inclusion disease.

Giles et al.[4] have suggested the possibility that some cases of infantile nephrosis may be due to an inborn error of metabolism. This postulate was occasioned by the finding of crystals in alcohol-fixed liver, spleen, bone marrow, and kidneys from three patients with infantile nephrosis. In addition, they noted severe cyst-like dilatation of the proximal tubules, with relatively little glomerular abnormality. The resemblance of these findings to those of cystinosis prompted these authors to suggest that a metabolic defect, manifested by the deposition of crystals, produced the tubular abnormality, which in turn caused the nephrotic syndrome.

Unfortunately, although we confirmed both the tubular abnormality and the crystallization which the British workers described, we were unable to confirm their interpretation of these findings. The crystals in the kidney and liver were found to be artifacts caused by alcohol fixation, and therefore add no support to the metabolic theory of etiology. In addition, the fact that the submicroscopic lesion of the glomerular epithelial cells in these infants is identical with the lesion found in older nephrotics indicates that the primary abnormality probably resides in the glomerulus rather than the tubule. We do not believe that the possibility of a metabolic defect as a cause of nephrosis should be discarded, but, at present, there appears to be no evidence in favor of this hypothesis.

Summary and Conclusions

The clinical and pathologic features of 12 children who developed nephrosis within the first year of life are presented. The symptoms, physical findings, and laboratory abnormalities were essentially the same as those of idiopathic childhood nephrosis. However, the cases of infantile nephrosis were characterized by a high familial incidence, refractoriness to treatment, and a high mortality rate.

Microscopically, the kidneys from five patients showed no glomerular abnormalities, while kidneys from four patients showed varying degrees of glomerular fibrosis. The kidneys from the remaining three patients were of special interest microscopically, since a striking degree of dilatation of the proximal convoluted tubule was found. No cause for this unusual pathology could be determined by microdissection of the kidneys.

Electron microscopic study of glomeruli from nine patients revealed fusion of the epithelial cell foot processes. This abnormality of fine structure was identical with the lesion observed to be characteristic of older patients with nephrosis. The presence of this alteration of fine structure in glomeruli from patients with severe tubular dilatation suggests that the primary abnormality in the various patients with infantile nephrosis resides in the glomerulus.

The possible etiologic factors are discussed, with emphasis on the possible role of maternal toxemia. We conclude that the autoimmune mechanisms, which have been given etiologic importance in childhood nephrosis, probably can not be implicated as the cause of infantile nephrosis. Further, the results of this study do not support the suggestion of other investigators that a metabolic defect, associated with crystalline deposits in the kidney, is the cause of infantile nephrosis.

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Bromide Space in Infants and Children

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Introduction

It is well established that when bromide is administered to a human or animal subject it exchanges rapidly with nearly all of the body chloride.[1-6] For this reason the volume of distribution of bromide is essentially the same as that of chloride, the exception being the cerebrospinal fluid. When bromide volume of distribution is multiplied by the chloride concentration in serum, the quantity of chloride obtained is that which exchanges rapidly with bromide, and may therefore be called "exchangeable chloride," although it is sometimes called "total body chloride" since the values are so nearly the same.[6-7]

Since the volume of distribution of chloride includes the extracellular fluid, connective tissue, skin, erythrocytes, and, to a minor extent, some other cells, the relationship between chloride (or bromide) space and total body mass will depend upon the composition of the body. When a large proportion of the body weight is fat, the bromide space will be a smaller proportion than it will be in a lean subject. When a person gains or loses weight, the composition of his body may change because of the gain or loss of fat, other tissue, or fluid; if fat is lost, bromide space will become a larger proportion of his weight, even if the volume of the space itself remains the same. In infants and children this situation is further complicated by the changes in the composition of the body associated with weight gained during growth.[8]

Many physiological functions seem to be more closely related to surface area than to body weight.[9,10] Furthermore, surface area is not affected by nutritional status or degree of hydration as much as weight alone. As Brody[9] (p. 632) says: "Higher animals grow not in one, two, or three linear dimensions, but in many. . . . This, of course, is the reason why weight cannot be expressed exactly as the cube of some *one* linear measurement, or that surface area cannot be expressed as the square of some *one* linear measurement, or even as the $\frac{2}{3}$ power of weight." When the Du Bois formula for surface area was applied to the infants and children in our own study, the surface areas of the infants were close to the 0.6 power of the body weight, while the oldest children's surface areas were close to the 0.7 power of the weight. This change in relationship during growth is similar to that calculated by Brody[9] (p. 447), who showed that several physiological functions, such as heat production and oxygen consumption, were related to the 0.7 power of weight in mature animals and to the 0.6 power of weight in the same animals during growth.

In the following study we were desirous of expressing the relationship between the bromide space and body size in a manner which would be as independent as possible of extraneous factors such as nutritional status, and we have therefore chosen to relate it to surface area. Our purpose in this investigation was first to define the relationship between bromide space and surface area in normal infants and children and then to compare with them values obtained from children who had rapidly gained or lost weight, as well as values obtained from newborn infants.

Material and Methods

The infants and children studied were patients on the pediatric wards or in the nursery. The 19

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normal subjects were convalescents who were not receiving medication and who had normal serum electrolytes. Fourteen normal newborn full-term infants, five premature infants, four children being treated with prednisone for rheumatic fever, and three children with nephrosis were the subjects for comparison with the normal. Age, sex, and race of these subjects are detailed in the various tables.

An approximately 5% sodium bromide solution was prepared and sterilized for intravenous injection. The volume administered was measured accurately and injected quantitatively. About 2 ml/kg. was the dose for normal subjects, and it resulted in a serum concentration of about 2.5 mEq/L. The exact bromide concentration of the solution was determined and the exact dose then calculated. Because of the difficulty of quantitative intravenous injection in the newborn infants, an approximately isotonic solution of sodium bromide (1.6%) was injected subcutaneously. The usual volume injected was 15 ml., and the dose was calculated as above. No effect of the bromide could be detected in 44 out of the 45 subjects; one newborn infant had a transient rash over the site of the subcutaneous injection.

When serial blood samples were collected from normal subjects, the serum bromide was constant between 2 and 24 hours after the intravenous injection of bromide. In the infants, serum bromide was constant between 18 and 40 hours after subcutaneous injection of the bromide. The fact that food intake was minimal during the first 48 hours of life may account for the constancy of the serum bromide in these infants, since it has been shown that fasted adult dogs maintain a constant serum bromide level for three days or more after a single intravenous injection.[11] We selected 3 hours after intravenous and 18-20 hours after subcutaneous injection as our routine sampling times, because equilibration seemed complete and no significant loss of injected bromide seemed to have occurred. A second later sample was obtained whenever possible.

Serum bromide was determined by the technique of Wolf and Eadie,[12] but the quantity of serum was reduced to 1 ml. of a 1:11 filtrate and the other reagents were reduced proportionately. Serum chloride was determined by the method of Schales and Schales.[13]

Bromide space was calculated as bromide injected divided by serum bromide concentration. Exchangeable chloride was calculated as serum chloride multiplied by bromide space. Surface area was calculated by the DuBois formula; this is most easily done with the aid of a nomogram.[10]

Results and Comment

The results obtained on 19 normal subjects are reported in Table 1. Graphic analysis showed that the relationship between bromide space and surface area is curvilinear on rectangular coordinates but linear on a double log plot. Calculation of the regression of the log of the bromide space (liters) on the logs of the surface area (square meters $\times$ 10) resulted in a regression coefficient of 1.2 and an intercept equal to the log of 0.6. Transformed into the curvilinear equation, this is expressed as: Liters $= 0.6(\text{sq. m.} \times 10)^{1.2}$. The surface

TABLE 1.—*Bromide Space and Exchangeable Chloride in Normal Infants and Children*

Name	Age	Race	Sex	Weight, Kg.	Surface Area, Sq. M.	Bromide Space, L.	Exchangeable Chloride, mEq
C. H.	7 wk.	White	M	4.3	0.250	1.97	186.5
C. S.	7 mo.	Negro	F	6.6	0.315	2.60	260
J. K.	7 mo.	Negro	M	6.2	0.305	2.44	250
T. G.	10 mo.	Negro	M	7.3	0.340	2.74	284
C. P.	11 mo.	Negro	F	9.6	0.410	3.82	386
C. M.	15 mo.	Negro	F	10.7	0.460	3.38	362
V. F.	3 yr.	Negro	F	9.6	0.480	3.44	353
M. H.	3½ yr.	Negro	F	12.5	0.570	4.58	458
V. W.	4 yr.	Negro	F	11.8	0.550	4.68	487
B. W.	4 yr.	Negro	F	12.7	0.560	4.77	500
V. S.	3½ yr.	Negro	F	15.2	0.622	5.00	487
E. G.	3½ yr.	Negro	M	17.5	0.690	5.40	567
H. S.	5 yr.	Negro	M	16.2	0.680	6.30	636
D. T.	4½ yr.	Negro	F	19.3	0.760	7.58	766
W. P.	6 yr.	White	F	18.5	0.780	7.78	763
G. D.	6 yr.	Negro	M	21.6	0.830	9.03	922
W. J.	8 yr.	Negro	M	24.7	0.940	9.17	863
W. S.	11 yr.	Negro	M	32.0	1.135	11.30	1020
R. B.	2½ yr.	Negro	M	10.9	0.480	4.18	397

area was expressed as square meters $\times 10$ simply to avoid the use of negative logs in the calculation.

Because our series was small, we examined the literature for data with which ours could be compared. Three papers were found dealing with exchangeable chloride in infants and children,[7,15,16] but only Cheek's [15] contained sufficient data for a calculation of bromide space. Cheek reported only sex, age, and weight of his subjects, and, since we wished to compare his results with ours, surface area was estimated as follows. Forty of his subjects whose weights were normal for their ages and whose serum chloride values were normal were selected. The heights of these subjects were estimated from age-height-weight tables [17-19] and their surface areas calculated from the DuBois formula. When these 40 points were added to our own 19, calculation of the regression of the log-log line gave the same regression coefficient of 1.2 and the same intercept at the log of 0.6. This close agreement between two independently collected groups of data lends strength, we feel, to our definition of the normal relationship. The standard deviation from regression was calculated on the basis of all 59 points. Figure 1 shows the curve constructed to fit the equation $y=0.6\times^{1.2}$ and the individual points on which the calculations were based.

Because it is cumbersome to calculate surface area from height and weight and then interpolate on the curve shown in Figure 1, the formula relating bromide space to surface area was combined with the DuBois formula relating height and weight to surface area, so that the relationship of height and weight to bromide space was expressed. A nomogram was constructed to solve this rather complex equation (Fig. 2), so that it is possible from the height and weight of a person to find the average normal bromide space for a person of that size directly from the nomogram. The average normal exchangeable chloride is obtained by multiplying the space by the average normal serum chloride, which is 105 mEq/L in our experience. If bromide space and serum chloride concentration are

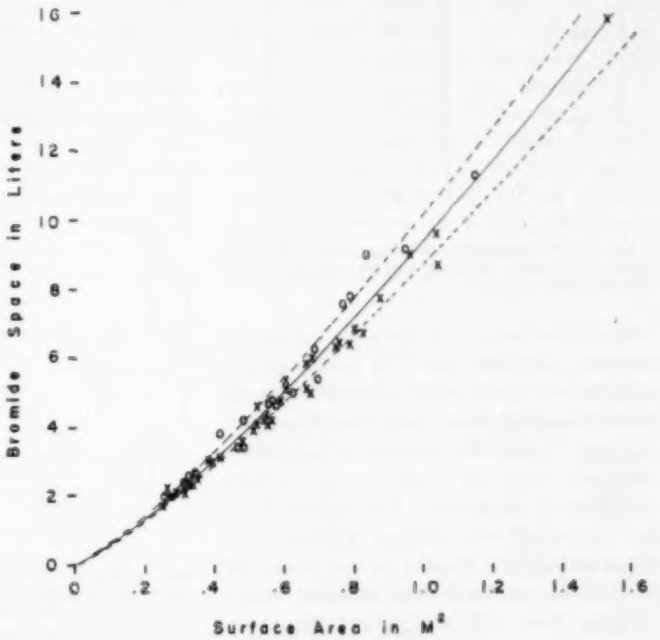

Fig. 1.—Bromide space in liters (ordinate) is plotted against surface area in square meters (abscissa). The solid line is the plot of the equation $y=0.6x^{1.2}$ which was derived from the regression of the log of y on the log of x and is the same whether only our 19 points or all 59 are used. The broken lines are derived from one standard deviation regression and may be expressed as $y\pm0.08y=0.6x^{1.2}$. All 59 points were used in this calculation. Circles represent our values for 19 normal infants and children; crosses, Cheek's values for 40 normal infants and children.

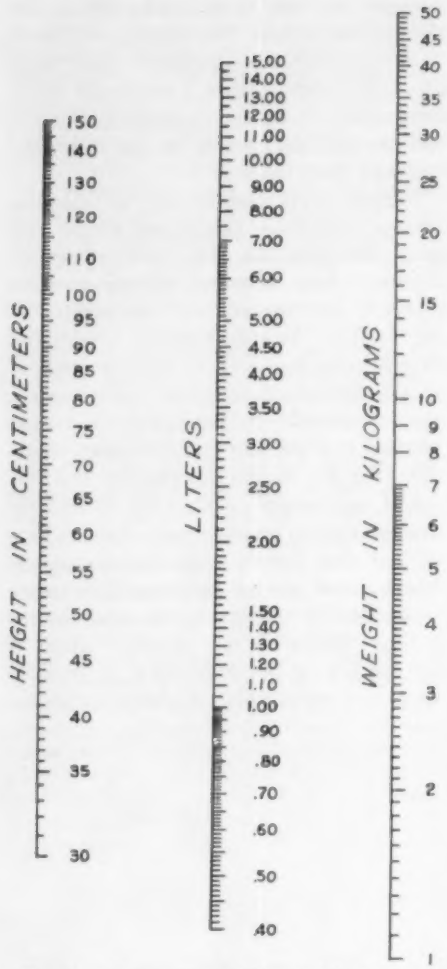

Fig. 2.—A nomogram relating height in centimeters and weight in kilograms to average normal bromide space in liters.

then determined, it is possible to decide whether chloride space or exchangeable chloride are significantly different from the average normal value. Since the nomogram can express only the average normal values, allowance must be made for a standard deviation of about 8%. The derivation of the regression and standard deviation was based on subjects ranging in size from 1.52 to 0.25 sq. m., and with bromide spaces ranging from 15.9 to 1.8 liters; the upper limit is nearly that of the average adult, but values below the lower limit remain to be validated.

Thirteen of the newborn infants who were studied during the first 48 hours of life had larger bromide spaces than would be expected if the nomogram is valid for subjects smaller than 0.25 sq. m. The data obtained are reported in Table 2 and shown graphically in Figure 3. Other techniques have indicated that the newborn infant has an abnormally large extracellular fluid volume,[20] and these infants may even appear clinically edematous. Since values for the oldest full-term infant (54 hours) and for five premature infants aged 2 to 18 days (Table 3) agree very closely with those obtained from the nomogram, it is possible that the nomogram does apply to subjects smaller than 0.25 sq. m. who are not in the first day or two of life.

After the normal relationship of bromide space to height and weight was defined, some abnormal subjects were evaluated for comparison. In cases of rapid weight gain, it is especially desirable to know whether the patient is accumulating excessive fluid and chloride. Determinations of bromide space and exchangeable chloride were, therefore, made on four children who were on long-term prednisone therapy for rheumatic fever. In one instance (M. S.) de-

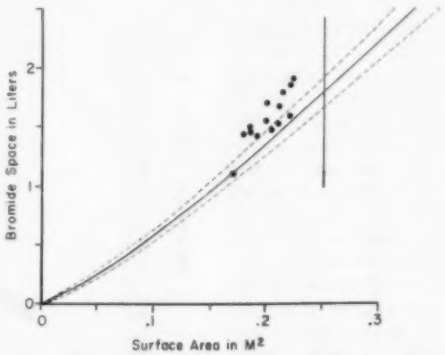

Fig. 3.—This is an enlargement of the lower portion of Figure 1. The vertical line indicates the lower limit of the data from which the equations for the curves were derived. The points are values for 14 normal newborn infants.

TABLE 2.—*Bromide Space and Exchangeable Chloride in Normal Full-Term Infants*

Name	Age, Hr.	Race	Sex	Height, Cm.	Weight, Kg.	Bromide Space, L.	Exchangeable Chloride, mEq
B.	26	Negro	F	48.0	2.74	1.46	153
O.	28	Negro	F	51.5	3.80	1.85	194
F.	30	Negro	F	50.0	3.32	1.49	157
J.	31	White	F	51.0	3.47	1.69	179
L.	31	Negro	M	47.0	2.70	1.44	152
McK.	31	Negro	F	48.5	3.12	1.42	150
M.	32	Negro	F	52.0	3.48	1.79	177
R.	32	White	F	52.0	3.74	1.90	200
P.	32	Negro	F	49.0	3.60	1.52	166
W.	33	Negro	F	50.0	2.80	1.53	151
F.	35	White	F	54.0	3.48	1.59	171
McC.	38	White	F	50.0	3.24	1.55	164
H.	43	Negro	M	50.0	3.24	1.68	175
A.	54	Negro	F	46.0	2.56	1.15	121

TABLE 3.—*Bromide Space in Premature Infants*

Name	Age, Days	Sex	Race	Weight, Gm.	Length, Cm.	Bromide Space, L. Observed	Bromide Space, L. Nomogram
W.	16	M	Negro	1,840	46	0.93	0.91
S.	14	M	Negro	1,800	45.5	0.89	0.88
B.	18	M	Negro	1,960	44.0	0.88	0.90
E.	5	F	Negro	1,980	44.7	0.92	0.915
B.	2	F	Negro	1,940	44.7	0.905	0.91

terminations were made after two weeks of therapy and again after therapy for two months; during the interval she had gained 5 kg., but her bromide space had increased by only 0.3 liter. The results of these determinations are compared with the values obtained from the nomogram in Table 4. It is apparent that the weight gained by these subjects was not primarily due to fluid accumulation.

In cases of nephrosis, however, a rapid gain in weight is nearly always due to the accumulation of excessive fluid in the body. It is not difficult to decide that the nephrotic with anasarca has an increased chloride space. However, attempts to measure volumes of distribution of injected substances in such a patient are complicated by the fact that equilibration with a large volume of ascitic fluid may be slow. In one nephrotic with anasarca on whom a paracentesis was done, we were able to show that equilibration of bromide was nearly complete in 2½ hours and that serum and ascitic fluid had equal concentrations of bromide 24 hours later. In a second nephrotic with anasarca, ascitic fluid was not obtained, but serum samples collected at two and a half and at eight hours after bromide injection had the same bromide concentrations, so equilibration was apparently complete at two and a half hours. The fact that bromide equilibrates this rapidly with large accumulations of fluid further validates the use of three-hour samples in nonedematous subjects.

The data obtained on three nephrotics are reported in Table 5. It is obvious that in cases of anasarca an estimation of the average normal from the nomogram is meaningless. However, in the case of C. C. a second determination of bromide space and exchangeable chloride was made several months later when he was free of apparent edema. In this case and in a second case (G. B.), comparison with the average normal values indicates that both space and

TABLE 4.—*Comparison of Bromide Space and Exchangeable Chloride in Children on Long-Term Prednisone Therapy for Rheumatic Fever with Average Normal Values Derived from the Nomogram*

Name	Age, Yr.	Race	Sex	Height, Cm.	Weight, Kg.	Bromide Space, L. Observed	Bromide Space, L. Nomogram	Exchangeable Chloride,* Observed	Exchangeable Chloride,* Nomogram
E. T.	11	Negro	M	145	42.5	13.9	13.0	1375	1365
M. Y.	10	Negro	F	135	42.0	10.5	12.2	987	1281
S. P.	6	Negro	F	113	23.4	7.17	7.7	688	809
M. S.†	5	Negro	F	115	20.2	9.27	7.4	881	777
M. S.	repeat determination			116	25.2	9.56	8.2	915	861

* An average normal serum chloride of 105 mEq/L was used.

† First data on M. S. after only two weeks of therapy; repeat determination after two months of therapy.

TABLE 5.—*Bromide Space and Exchangeable Chloride in Children with Nephrosis*

Name	Age	Race	Sex	Height, Cm.	Weight, Kg.	Bromide Space, L.		Exchangeable Chloride, mEq	
						Observed	Nomogram	Observed	Nomogram
M. A.	15 mo.	White	F	80.0	16.5	11.5	(anasarca)	1242	(anasarca)
C. C.	6 yr.	Negro	M	122.0	41.0	28.2	(anasarca)	2876	(anasarca)
C. C. repeat determination				125.0	25.0	13.1	9.0	1221	945
G. B.	6 yr.	Negro	M	115.0	20.7	11.1	7.4	1066	777

chloride values are large, even though no edema was evident in these patients.

Summary

The relationship between bromide space and surface area in normal infants and children between the ages of 6 weeks and 15 years has been described. So that calculation of surface area may be omitted, a nomogram has been constructed showing the relationship of bromide space to height and weight. Given the height and weight of an individual, the average normal bromide space may be determined from this nomogram, and the average normal exchangeable chloride may be calculated. Deviations from the average normal values may be detected by a comparison of the determined values with those derived from the nomogram.

Although full-term infants in the first 48 hours of life had larger bromide spaces than those shown by the nomogram, six older but smaller infants had spaces agreeing with the nomogram very closely. It is possible, therefore, that the nomogram may be valid for subjects smaller than 0.25 sq. m.

Evaluation of other patients showed that long-term prednisone therapy in rheumatic fever patients did not cause an increase in bromide space and that two nephrotics had larger than normal spaces even when they were not clinically edematous.

We are grateful to the pediatric house staff for their cooperation in our study of patients on the pediatric service and to Mr. W. T. Sute and Mrs. Grace W. Johnson for preparation of the nomograms.

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Acute Torticollis in Pediatric Practice

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Torticollis, or wry neck, is a condition in which the patient's head is tilted to one side in such a manner that the chin tends to point toward one shoulder and the occiput toward the opposite shoulder. The abnormal position of the head in cases of acute torticollis is due to the unequal contraction of the neck muscles, particularly the sternocleidomastoids. Acute torticollis in pediatric cases has received little attention in the literature compared with the many papers concerned with congenital torticollis.[1-4] A description of the various forms of acute torticollis and their differentiation follows.

Postural Torticollis

Postural torticollis may be found in the newborn, is acquired in utero, occurs infrequently, is usually *not* painful, and is *not* associated with a sternocleidomastoid tumor. Stretching the affected sternocleidomastoid by passively rotating the head each day for a limited period of time corrects this type of wry neck.

Postural torticollis in older children may occur from awkward, prolonged maintenance of the head in a position causing undue neck strain; for example, while sleeping, watching television, movies, or reading. This type of torticollis tends to be acutely painful. Its treatment will be discussed later in this paper.

Torticollis Secondary to Otitis Media

Middle-ear infections, if severe, may cause a child to have much pain and hold the head in a position of greater comfort. In these situations, the head is usually tilted as in wry neck. After maintaining the head in this position, the child may develop a torticollis of the postural type which causes additional pain. The tensely contracted sternocleidomastoid muscle would serve as a clue in determining to what extent the torticollis contributes to the patient's pain.

In cases of otitis media it may be difficult to determine whether a labyrinthine disturbance contributes to the wry neck, unless dizziness, nystagmus, head rolling, stepping gait, or falling were also present. Further study of the patient would be indicated if labyrinthine symptoms persisted after relief of acute torticollis.

Ocular Torticollis

Ocular torticollis occurs as a result of the patient attempting to fuse double images. For example, the child may have a strabismus which may not be manifest to casual observation. In an attempt to fuse the double image, he may shut one eye, or turn one eye inward or outward, or tilt the head to level the images.[5] If the patient keeps the head tilted long enough, one of the sternocleidomastoid muscles may develop a sustained contraction with resulting pain and discomfort. The presenting complaint may be an acute "pain in the neck," whereas the primary pathology is in the eye muscles. However, one must bear in mind that a patient may have eye muscle pathology which is under corrective treatment and develop an apparently unrelated acute acquired torticollis. In instances of ocular torticollis, the patient may experience acute recurring pain and sternocleidomastoid muscle spasm from chronic ocular muscle pathology. Paresis of ocular muscles may also cause chronic torticollis with associated chronic thickening of the sternocleidomastoid muscle.[6]

In a series of 164 cases of brain tumors in children, it was found that squint or

diplopia was present in 26% of supratentorial and 29% of infratentorial tumors.[7] The patient who is suddenly discovered to have a squint, diplopia, or a compensatory torticollis subsequently will have other additional symptoms or findings if a brain tumor is the cause. These findings impress one with the importance of a complete physical examination of the patient who is being treated for acute torticollis apparently due to ocular muscle pathology.

Allergic Torticollis

Allergy as a cause of acute torticollis has been reported in one paper in three adult patients.[8] The belief was expressed that the torticollis was relieved by removal of the offending allergens. This has not been reported in other papers in adults or children.

Muscle Injury

Trauma sustained directly to one of the sternocleidomastoid muscles by a fall or blow can produce a hematoma or torn muscle fibers which may cause muscle contraction and the clinical picture of painful wry neck. Sometimes the trauma involves other neck muscles, such as the posterior capitis group, and the sustained contraction may cause severe pain with marked torticollis.

Suppurative Cervical Adenitis

Cervical adenitis with suppuration as well as cellulitis of the neck and underlying muscles may be associated with torticollis. If the primary infection is in the peritonsillar, pharyngeal, or maxillary sinus spaces, the lymphatic drainage to the cervical lymph nodes may cause an adenitis with resulting contractions of the underlying muscles.[9]

Normal children or children with minor pharyngeal infection may have detectable cervical adenopathy. In these instances it would be difficult to be certain if the mild adenitis is the cause of the torticollis.

Hess, Bronstein, and Abelson [10] reviewed the literature up to 1935 and described two of their cases under the title, "Atlanto-Axial Dislocations, Unassociated with Trauma and Secondary to Inflammatory Foci in the Neck." Their excellent paper demonstrated that infections of the neck may cause torticollis. They also believed that in these two cases of torticollis they were dealing with true subluxations.

Torticollis Secondary to Subluxation

The concept of cervical subluxation as a cause of acute torticollis, unassociated with trauma, has influenced the management of torticollis for many years.

Atlas-axis dislocation, or other dislocations of the cervical vertebrae have been described as a cause of acute, painful torticollis.[11] The entire question of subluxation of the cervical vertebrae in cases of torticollis, however, remains unsettled. Caffey states: "The roentgen findings are inconclusive in many cases when diagnostic clinical findings are present; the most significant clinical signs include limitation of movement of the spine with the head tipped toward the affected side and the chin rotated toward the opposite side. In such circumstances, traction relieves the patient despite the absence of roentgenographic changes of diagnostic significance." [12]

Townsend and Rowe reported observations of four children "with typical clinical findings of forward subluxation of the upper cervical vertebrae on clinical examination. This diagnosis was confirmed by roentgenographic examination of the cervical spine. The clinical status of each patient improved under therapy, but the roentgen changes failed to show comparable improvement or, at times after initial realignment of the vertebrae, showed reversion to the pretreatment positions without the reappearance of clinical symptoms." [13]

Of Townsend and Rowe's paper, Caffey states: "This is an important contribution, and the full appreciation that forward displacement of the second on the third cervical vertebra is a normal variant should prevent much unnecessary treatment in the vague diagnostic field of ventral and ro-

tatory subluxations of the infantile and juvenile cervical spine." [12]

Bailey also has reported: "In lateral roentgenograms of the cervical spine in adults, with the neck held in mild flexion, some 'step-off' is normally seen, i.e., the body of each vertebra is displaced slightly anteriorly with respect to the subjacent one. Infants and children show the same normal finding when the neck is held in mild flexion, especially at the level of the second and third cervical vertebrae, where there may be a step-off of as much as to 2 to 3 mm." [14]

Martin reported four cases of atlas-axis dislocations following cervical infection. He described the condition as starting with an infection, with resultant hyperemia and secondary vertebral decalcification. It was his belief that the lateral articular facets (one or both) of the atlas had slipped forward, causing a "locking" which resulted in wry neck.[15]

Donaldson, in 1956, reported 37 cases of acute acquired torticollis in children and young adults.[16] His paper contains the only large series of cases reported to date, with the exception of this study. Donaldson stated that proper roentgen examination is essential for the study of acute torticollis. His two commonest findings were a unilateral subluxation between vertebrae C-2 and C-3 and a rotary subluxation between the atlas and the axis, and the two lesions sometimes coexisted. Traction and manipulation were recommended as the treatment of choice. He believed that "the anatomic location and age distribution of these subluxations are partly explained by the obliquity of the articular surfaces, but other factors remain to be discovered." In his conclusions, he added: "I have found no definite answer to the question of why torticollis occurs as a result of injury in some children and does not so occur in others."

Others have reported the following conditions to be associated with acute torticollis: forward dislocation of the axis, unilateral dislocation of the atlas on the axis, fracture of the axis and crush fracture of the lateral mass of the axis vertebra,[17] and acute subluxation of the atlantoaxis articulation secondary to arthritis.[18] Thus, the problems associated with roentgenographic examination, problems concerning normal displacement variants of the cervical vertebrae, and lack of comparable roentgenological improvement after clinical improvement under therapy would seem to raise some question about the presence of true cervical subluxation in some of the cases of reported torticollis considered to be secondary to such subluxation.

Case Material

During the period 1949-1958 I have treated 46 cases of acute torticollis in my pediatric practice. The records of these patients have been assembled for presentation and summary.

Data obtained from this series relative to history are shown in the Table.

In 14 patients there was a clear-cut history of trauma; for example, following manipulation of the neck in a neurological examination, following a "Tilt a Whirl" ride in an amusement park, the usual "roughhouse play" of growing boys, swimming or diving accidents, trauma occasioned by a fall from a moving automobile, fall down a flight of steps, a fall striking the neck against furniture, and a fall due to fainting. Eighteen patients had evidence of infection at the time of examination, such as fever, upper respiratory infection, cervical adenitis, otitis media, pharyngitis, or tonsillitis. Two of these patients also had a

History in Cases of Trauma

History of trauma	14
Evidence of infection	18
Presence of strabismus	2
No obvious cause	15
Total	49 *

* This total differs from the number of cases since in two cases trauma was involved with infection, in one case strabismus with infection and each cause has been listed separately.

history of trauma. One patient had strabismus, which may have been of etiological importance, since he had neglected to wear his glasses the day previous to the onset of the torticollis. One patient had strabismus and also a fever of undetermined origin.

In 15 cases there was no unusual history prior to the onset of the wry neck. The evaluation of a history of trauma and its relation to the clinical picture of acute torticollis is difficult, because children are normally active and engaged in play that frequently exposes them to possible trauma. If the time relationship between trauma and symptoms of acute torticollis is relatively short or immediate, the cause and effect may be and often are readily surmised by patient, parents, and physician. Although a "cause and effect" history may be obtained, the severe symptoms may not appear until an overnight "latent" period. Several histories may serve as illustrations.

A 15-year-old boy recovered from nonparalytic poliomyelitis in August, 1951. Six weeks after the onset of the disease, an intensive neuromuscular examination revealed no abnormalities or sequelae of poliomyelitis. The day following the examination, the patient developed an acute wry neck that responded to ordinary therapy, i.e., local heat, rest, and acetylsalicylic acid. No other history could be elicited to account for the wry neck, and this case was thought to be caused by trauma occasioned by a vigorous neuromuscular examination.

Although a history of trauma may be clear-cut, other factors elicited in the history may cause the clinician further to investigate etiological factors. The following case histories illustrate this problem.

A 4½-year-old boy, January, 1949, presented himself with an acute wry neck immediately following "roughhouse" play with his brothers. Because of severe pain, he was given codeine. Relief was not immediate, but was complete and permanent the same day. A history was also obtained that one of the patient's brothers was currently being treated for tuberculosis of the spine. An x-ray of the patient's cervical spine was therefore ordered, and was reported as negative, as was a skin test of old tuberculin 1:1000.

A 3-year-old boy, March, 1956, fell from a moving automobile five days prior to being examined by me. Codeine was prescribed for the severe pain of acute torticollis. Relief was immediate and pain did not recur. X-rays of the cervical spine were requested because of the unusually severe trauma, and these were reported to be negative.

In certain cases it is difficult to evaluate the relative importance of several factors which may precede the appearance of torticollis. The following case illustrates such a situation.

A 2-year-old boy was brought to me in January, 1955, because of a wry neck following a "fainting" episode. Examination revealed that the patient had a moderately severe upper respiratory infection with cervical adenitis and a wry neck. The patient responded to therapy of local heat to the neck, rest, and acetylsalicylic acid. There was some question in my mind whether the fainting episode caused enough trauma to produce the wry neck or whether the cervical adenitis constituted the major cause.

One may speculate that a traumatized sternocleidomastoid muscle, previously irritated by infected lymph nodes, may be more than normally susceptible to injury and spasm.

In the absence of a history of trauma and evidence of infection at the time of examination, such as fever, upper respiratory infection, cervical adenitis, otitis media, pharyngitis, or tonsillitis, the etiology of a given case of acute torticollis is often obscure. The following case illustrates a less common cause for acute torticollis.

An 8-year-old boy was brought to my office, April, 1954, in a state of acute agony. The child was carried into the office by his parents, his mother carrying the patient under the arms and the father supporting the legs. The patient was in such excruciating pain, because of acute torticollis, that he refused to walk or even move as he lay on the examining table. The patient was given ½ grain (30 mg.) of codeine subcutaneously and was tested for ability to perform neck movements such as the "chin to shoulder" test, at 10-minute intervals. The patient obtained complete relief in approximately one-half hour and walked out of the office unassisted. A follow-up inquiry revealed no further symptoms. The only history obtainable was that the patient had played baseball the previous day, but there was no unusual traumatic incident recalled. Of interest was the fact that the patient, who ordinarily wore glasses for the correction of strabismus, did not wear his glasses on the day he had played baseball. Examination confirmed his strabismus, and he was advised to wear his glasses in the future during any type of activity.

Difficulties that may occasionally arise for a clinician in making a differential diagnosis of acute torticollis are illustrated by the following cases.

An 8-year-old boy was seen, March, 1950, with a "stiff neck" and a healing traumatic lesion of the right foot. Tetanus had been suspected and hospitalization was advised. My examination revealed marked spasm of the left sternocleidomastoid muscle. An excellent response occurred in two days with local heat to the neck, pentobarbital (Nembutal) and acetylsalicylic acid.

A 4-year-old girl was under the care of her family physician for gastroenteritis with severe vomiting for four days. The patient developed a painful "stiff neck," and meningitis was suspected. Physical examination on consultation, March, 1958, revealed bilateral sternocleidomastoid muscle spasm and muscle spasm at the base of the neck. It was noted that the patient was relieved of her pain and spasm when the head was extended backward. She kept her head in this position for comfort. Kernig and Brudzinski signs were negative. Treatment with meprobamate (Equanil, Wyeth) 200 mg. t.i.d., acetylsalicylic acid, local heat to the neck, and a combination of dihydrostreptomycin and penicillin (Combiotic, Pfizer) intramuscularly were prescribed with an uneventful recovery from the torticollis in a few days.

As shown in the Table, no obvious cause could be found in 15 cases. It is speculated that acute torticollis may be similar, or related to epidemic myalgia, or Bornholm disease. This illness, caused by a Coxsackie virus, affects children by causing muscular pain, chiefly at the costal margins and in the substernal region and less often in the back, shoulders, abdomen, or hips. Pain is induced by voluntary or reflex contraction.[19]

Rather typical of this group is the case of a girl of 5 years and 3 months, who was seen November, 1953, with severe pain in the right side of the neck. Physical findings were negative except for spasm of the right sternocleidomastoid. There was no history of antecedent infection, trauma, ocular pathology, central nervous system involvement, or evidences of other possible etiology. She was given 15.0 mg. of codeine subcutaneously because of her severe pain. Relief was almost complete before she left the office, and there was no recurrence.

Analysis of Signs and Symptoms of Acute Torticollis in Infants and Children

In a series of 46 cases which I observed, the clinical picture of acute torticollis was very impressive. There was always a great amount of pain, which was often associated with cervical muscle spasms. Any active or passive attempts to move the head from the "position of comfort" precipitated muscular spasm and thus more pain. Any change in body position which turned the head or placed tension on the involved cervical muscles was resisted by the patient. Neck pain was a prominent symptom in my experience, although this is frequently not emphasized by others. In fact, in a popular pediatric textbook, it is stated that pain does not occur in torticollis.[20] It is entirely possible, however, that less painful or painless cases of wry neck may not lead the patient to seek medical attention.

An older child often would support his head with his hands in an attempt to "carry" his head without causing undue strain on the cervical muscles. Patients are afraid to lie down or sit up, once they assume a position that causes the least discomfort. In the majority of cases the grotesque appearance of these patients allows one to make a diagnosis of "wry neck" on sight. Many have so much pain that they want to be left alone in a huddled position.

The presenting complaint usually is "pain in the neck," or "stiff neck." In the younger children, the mother will note the unusual position of the child's head and marked irritability, to which they may refer as a "cross" disposition.

There was palpable evidence in all cases of a tense sternocleidomastoid muscle on one or both sides. The tenseness of the sternocleidomastoid muscle may be likened to a "piano wire." In the severer cases it was suspected that other cervical muscles were involved, but it was difficult to evaluate the extent of involvement under the circumstances as described in this clinical picture. Cooperative older children, when questioned, may indicate that the pain and spasm also involve the upper thoracic spinal area.

The most helpful sign which can be elicited is the "chin to shoulder test." If

the patient is asked to rotate his head, so his chin touches his shoulder, he can readily do this maneuver on the side of the contracted sternocleidomastoid muscle. When asked to rotate his head to the other side and attempt to touch his chin to his opposite shoulder, he usually has an exacerbation of pain with limitation of movement, sometimes not beyond the midline. Rarely muscle spasm is bilateral and severe and the "chin to shoulder" test may not be readily elicited, or the patient's head may be flexed forward, giving the clinical appearance of so-called "forward subluxation" of the cervical vertebrae. In the 46 cases presented, however, all but one gave the clinical appearance of so-called "rotary" or "facet subluxation," with typical "wry neck" symptoms including a positive "chin to shoulder test." One case, previously cited, had the appearance of so-called "forward subluxation" with bilateral neck muscle spasm, including spasm of muscles at the base of the neck. It was noted that she was somewhat relieved when the head was extended backward.

Management of Acute Torticollis in Infants and Children

In reviewing the management of the 46 cases in this series, it was found that the patients received various medications, according to the degree of pain manifested. Of the first 38 patients in this series, 29 received codeine because of the severity of pain. Nine received no codeine since pain was not as severe.

The last eight patients in this series, treated in 1958, received no codeine for pain, even though pain was severe. These latter patients received meprobamate in seven instances and methocarbamol (Robaxin, Robins) in one instance.

I have found codeine to be of great value for the management of the pain and discomfort of acute cases of torticollis. In fact, dramatic results were witnessed in the office or home, 5 to 15 minutes after injection of codeine in those cases wherein it was used in this series. Furthermore, a comfortable child is more amenable to further examination and treatment. There are few instances in pediatric practice that can match the gratifying results from the judicious use of codeine as when used for selected cases with the painful manifestations of acute torticollis. Whether the predominant cause of the acutely painful torticollis is ocular, infectious, or traumatic, the relief from pain reduces or eliminates the muscular spasm, and oral codeine medication for one day is frequently all that is necessary for pain relief. After the cycle of "pain-spasm-pain" is interrupted, specific measures may be instituted to treat the basic cause of the torticollis.

Children seem to tolerate codeine very well. A suitable dose is 8 to 15 mg. of codeine given subcutaneously as determined by a consideration of the weight, age, and severity of pain. The 6- to 12-year-old child can tolerate 15 to 30 mg. subcutaneously with excellent results. No adverse effects of codeine were noted in the 29 cases of this series in which it was used.

Pupillary constriction is a good index of the codeine action. After the appearance of pupillary constriction, the "chin to shoulder" test may be tried at varying intervals to determine the effectiveness of the codeine to relieve pain.

Because of the popularity of the "muscle relaxants" and "tranquilizers" and favorable reports about their use in instances of muscle spasm, I attempted to use them in the last eight cases treated in 1958.

A 7-year-old boy was seen by me with the complaints of recurrent ear trouble, poor appetite, tonsillitis, and mouth breathing. Examination revealed the presence of a moderately painful wry neck. The cause of the wry neck appeared to be a cervical adenitis secondary to tonsillitis. Response was good to meprobamate 200 mg. b.i.d. and local heat to the neck.

A 20-month-old girl was seen by me with a very painful left wry neck of unknown etiology which had been present for approximately four days. This is the only instance in this series wherein methocarbamol was used. One-half tablet, or 0.25 gm., t.i.d. was prescribed for two days. The mother

reported the patient's relief of pain and muscle spasm in one day.

These are typical of the eight cases in which "muscle relaxants" were used in this series. The results are very gratifying and warrant further trial in the treatment of acute torticollis in pediatric practice. The medication is given orally, and the effects of its action are slower than when codeine was used by injection. Relief with these relaxants was obtained generally in 14 to 48 hours.

Psychogenic factors must be considered with children. Acute torticollis accompained by pain which is not readily relieved may produce a fearful child. In the presence of a neurotic mother-child relationship, or some neurotic elements in the patient's personality, psychiatric symptomatology may become more evident during the child's painful illness. Thus, the clinician should be aware of possible emotional "overlays" in managing these problems. A great deal of comforting reassurance must be given the child in the acute distress of painful torticollis. The patient is aware of the pain of any head movement and is reluctant or hesitant to move the head even after the pain has been greatly minimized or completely relieved.

Most cases are seen relatively early in the course of the disease, if there is physical distortion and pain. The general public's awareness of the possible implications of a "stiff neck" or "pain in the neck," especially in "poliomyelitis-conscious" areas, may also account for their seeking medical aid early. The parents are frequently anxious, and, when discussing the illness with them, the physician may find the older, more descriptive term "wry neck" more satisfactory than the term torticollis. This may also simplify discussion of the cause and management. Parents should be forewarned that moderate stiffness or vague discomfort may persist several days after the initial therapy.

The examining physician should carry out a neurological evaluation which is necessary to rule out central nervous system pathology that may cause torticollis. This important evaluation can be accomplished satisfactorily with a cooperative patient who is not in too great pain.

Local heat to the neck, acetylsalicylic acid, and antibiotics are used as indicated. For ocular torticollis, the patient should have one eye covered with a patch for temporary relief and referred to an ophthalmologist after the acute episode has terminated. Known cases of strabismus corrected by glasses should be induced to wear their glasses as a necessary part of their therapy.

Certain laboratory examinations are recommended, particularly if the history or physical examination does not yield sufficiently clear information to warrant a diagnosis. This is especially true in instances of severe trauma, arthritis of the cervical spine, tuberculosis, or chronic pathology of the neck resulting in acute torticollis. Peripheral neurological symptoms or findings suggestive of cord or nerve root pressure are prime requisites for x-ray studies. Clinicians who subscribe to the theory that acute torticollis in children is often accompanied by subluxation of the cervical vertebrae may routinely order such x-ray studies.

In the present series of 46 cases, x-ray studies were postponed in instances of acute torticollis, especially when due to cervical adenitis, pharyngitis, otitis media, ocular muscle paresis, direct sternocleidomastoid muscle trauma, or postural strain. Where definitive diagnosis was made and appropriate therapy appeared successful, x-ray studies were not carried out. X-ray studies were also not carried out where etiology was unknown and conservative therapy was successful with no evidence of recurrence on follow-up. Such studies were invariably carried out where there was a history of moderate or severe trauma. Traction of the cervical spine by the use of a head halter is indicated when conservative medical measures have met with failure, or when there are neurological or orthopedic

indications for this type of therapy. Fracture, subluxation, or evidence of cervical cord or nerve root pressure are examples of indications for such traction therapy. In no case in the present series as treated by me was traction utilized.

Comment

The concept of subluxation of cervical vertebrae as a cause or a result of torticollis is open to question. Furthermore, recent roentgenological evidence does not support the concept of subluxation and, herein reported, all 46 cases were successfully treated without traction.

The exact mechanism of acute torticollis is not understood. A theory concerning it which we would like to propose is that the sequence of events is based, at least in part, on static and statokinetic reflexes. Reflex mechanisms governing the orientation of the head in space, the position of the head in relation to the trunk, and the appropriate adjustment of limbs and eyes to the position of the head, are called into action by afferent impulses discharged from receptors situated in (*a*) the vestibular apparatus, (*b*) the neck muscles, (*c*) the retina, or (*d*) in the body wall or limb muscles.[21]

Righting reflexes may be demonstrated in a baby a few weeks old. When lying prone, the infant raises his head into a nearly vertical position. When the infant is blindfolded and held by the pelvis in different positions in the air, the head is moved toward the normal position.[21]

The severe pain that results in acute torticollis is aggravated by these righting reflexes that are in constant operation to maintain the head in proper relation to the neck and trunk. Thus, the sustained contraction of the muscles, whether due to strain, direct trauma, irritative phenomena from toxins, pustular discharge, or virus infection, causes a vicious cycle of "pain-spasm-pain." Added to this may be a pull by opposing muscles acting in the dynamics of the statokinetic reflex which serves to intensify the "pain-spasm-pain" cycle. When the cycle is broken, the normal proprioceptive reflexes of the neck muscles bring the head back to the normal relation with the trunk.

In effect, any irritative phenomenon of the neck muscles, lesions of the brain involving the vestibular pathway, ocular muscle paresis, cortical or cerebellar lesions can cause torticollis.

Summary

Acute torticollis in pediatric practice may be commonly of the traumatic, infectious, or ocular type, but just as commonly the cause cannot be readily ascertained.

Subluxation of cervical vertebrae as a common cause of acute torticollis is questioned.

Neck pain is a prominent symptom of acute torticollis in children.

Conservative medical management as used in this series of 46 cases is presented.

Dr. Leon J. Epstein, Chief of Research, California Department of Mental Hygiene, assisted in the preparation of this manuscript.

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Preparation of P^{32}-Labeled Candida Albicans

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Introduction

Determination of the route of infection and method of transmission of pathogenic organisms from one host to another has so far been a matter of inference rather than exact proof, since there is no way of distinguishing a given strain of a pathogen from other strains of the same species or type.

"Tagging" an infectious strain with radioactive material in order to render it distinguishable from others of the same species might offer a means of tracing such an organism through successive hosts.

It was therefore attempted to prepare a "tagged" pathogen, and to determine the length of time through which radioactivity would remain detectable in vitro in successive subcultures from the original labeled strain. Candida albicans, the etiologic agent of thrush, was used for these experiments.

Radioactive phosphorus (P^{32}) was chosen as a "label," since it is a beta rather than a gamma emitter, with a maximum tissue penetration of only about 8 mm.[1] This greatly increases the safety of handling and testing exposed materials.

Procedure

A pure culture of C. albicans was grown on Sabouraud's agar for 48 hours at 37 C. The growth was washed off with, and suspended in, 5 ml. of sterile saline. Of this suspension 1 ml. was introduced in each of three culture tubes containing per tube 10 ml. of Sabouraud broth and sufficient radiophosphate ($NaH_2P^{32}O_4$ and $Na_2HP^{32}O_4$) to give a radioactive strength of 10μc. per milliliter of culture medium.

After 48 hours' incubation at 37 C the growth in each tube was washed with saline and centrifuged seven times in order to remove all traces of the culture medium. A negative Molisch reaction was taken as an indication that the glucose-containing medium had been removed.

Each of the three resulting sediments was resuspended in 3 ml. of saline. One sample was sealed into an ampule and used for counting; the second was used for autoradiographs, and the third was used for subculture to nonradioactive Sabouraud broth.

The same procedure was repeated for six consecutive subcultures made at 48-hour intervals. Each subculture was made in triplicate, one tube being used for counting, one for autoradiographs, and one for the next subculture.

The entire experiment was performed twice, with two different strains of C. albicans.

Radioactivity counting was done by means of a gas-flow counter. Three counts were performed on each of the total of seven samples: one on the entire suspension, one on the precipitated cells, and one on the supernatant after a final centrifugation.

Autoradiographs were prepared from smears of the seven samples by means of the melted emulsion technique of Messier and Leblond,[2] using Ilford G5 Nuclear Emulsion Gel. This was done in order to corroborate, and possibly replace, the counter method, and to preserve a permanent record of the experiments.

In order to detect possible modifications of the characteristics of C. albicans due to radioactivity, tagged and nontagged strains were compared with regard to growth rate, microscopic morphology, chlamydospore formation, fermentation reactions, and animal pathogenicity.

Results

There was no appreciable difference between a freshly tagged and a nontagged strain of C. albicans with regard to the

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TABLE 1.—*Comparison of Species Characteristics in "Hot" and "Cold" Strains of Candida Albicans*

Reaction Tested	"Hot" Strain	"Cold" Strain
Fermentations, 5 Days		
Glucose	A/G	A/G
Maltose	A/G	A/G
Sucrose	A	A
Lactose	0	0
"Budding time"	120 min.	110 min.
Chlamydospores	+	+
Average colony diameter, 48 hours	5.6±0.9 mm.	5.2±0.8 mm.
Mouse pathogenicity	+	+

species characteristics tested. As shown in Table 1, both cultures exhibited a similar growth rate under similar conditions of incubation. Microscopic observation at 30-minute intervals over a period of 3 hours revealed that both strains formed new buds on the average of every 110 to 120 minutes. This observation agrees with findings obtained for Saccharomyces cerevisiae.[3,4]

There was no significant difference between the average colony diameter of six "hot" and six "cold" cultures on Sabouraud's agar after 48 hours' incubation.

Both organisms gave the same fermentation and assimilation reactions.

Both formed abundant chlamydospores within 24 hours on Cream of Rice-Tween 80* agar.[5]

Both caused subcutaneous abscesses in mice when injected by Selye's air-pouch technique.[6]

* Polysorbate 80.

Positive autoradiographs, recognizable by a "halo" of reduced silver particles radiating from "hot" cells, were obtained from the original labeled culture, and from four successive subcultures grown on cold media. These visual findings were confirmed by the results obtained from the corresponding samples tested in the gas-flow counter.

It will be noted from Table 2 that the radioactivity, as measured in counts per minute, diminished in a straight-line progression, and that none was detected in the last two subcultures. This decrease in the number of "hot" cells was also clearly visible in the autoradiographs.

As regards transmission of radioactivity, therefore, approximately 120 generations, descended within 10 days from the original tagged culture, were still radioactive, as calculated on the basis of one generation (1 bud) being formed every 120 minutes. Autoradiographs prepared from stained sections of mouse tissue infected with the tagged strain were strongly positive after eight days and clearly indicated the location of the tagged organism.

It may be concluded from these preliminary experiments that a P^{32}-tagged strain of C. albicans remains detectable in the original host for at least 8 days, while transmission of radioactivity in vitro can be traced over a period of 10 days, each successive subculture representing a different "host" in the chain of "infection."

By using this technique, the authors have successfully traced the transmission of a

TABLE 2.—*Radioactivity of Successive Candida Albicans Subcultures Descended from Stock Culture Labeled with P^{32} (10 μc/ml. of Medium)*

	Gas-Flow Counter				
Sample No.	Net C/M Supernatant	Net C/M Cell Suspens.	Corrected * C/M/50λ Cells	Net Corrected C/M/ml. Cells	Autoradiograph
Stock Culture	14,686	77,308	62,628	1,252,440	+
Subculture I	2,061	20,899	18,818	376,360	+
II	623	6,753	6,130	122,600	+
III	152	2,074	1,922	38,440	+
IV	0	339	339	6,796	+
V	0	0	0	0	0
VI	0	0	0	0	0

1,000λ=1 ml.

* Figures corrected for background count.

tagged strain of C. albicans from vaginally infected pregnant mice to their newborn offspring.[7]

Summary

In order to establish a possible means for tracing a given infectious organism through successive hosts, a strain of Candida albicans was labeled with radiophosphate and the radioactivity was traced through approximately 120 generations in vitro. The organism did not appear to be affected by the radiation and retained its species characteristics.

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Composition of Milk of the Marsupial Trichosurus Vulpecula

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Preface

My interest in the opossum young as ideal animals for research in selected problems of human premature infants was pointed out in this journal in 1957. Two years previously I began correspondence with Dr. Bolliger which resulted in his undertaking, with Dr. Gross, the study based on the Australian "possum," now reported in this journal. The persistence with which they pursued this problem, and their ingenuity in obtaining young at different stages of development; in devising special apparatus for collecting minute amounts of milk, and in selecting appropriate methods for its analysis should stimulate other researchers to find ways and means to utilize the opossum for research.

The data presented by Gross and Bolliger on changes in the composition of the maternal milk during growth of the young will, I think, be of special interest to pediatricians in connection with the nutritional requirements of premature infants in the neonatal period.

It is my hope that further studies to throw new light on clinical problems of prematurity may be undertaken in this country, using the American opossum, Didelphis virginiana, as the experimental animal.

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The first analyses of marsupial milk were reported by Bolliger and Pascoe (1953). However, only eight specimens from three kangaroos (Macropus robustus) with large young could be examined, and it was obvious that further data were required from this or some other marsupial to gain more insight into the chemical composition of the milk of metatheria with their unique second extrauterine period of gestation in a pouch formed by skin. At the suggestion of Dr. Ethel C. Dunham, the milk of a smaller marsupial (Trichosurus vulpecula), the common brush-tail phalanger, or Australian opossum, was examined.

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Remarks on Suckling and Collection of Milk Samples

After a short period of gestation of about 20 days, the female of T. vulpecula with a body weight of 1.5-2.0 kg. delivers a single offspring, which immediately after birth proceeds to the pouch. In the newly born "pouch embryo," which measures about 1.5 cm. in length and weighs less than 0.5 gm., the mouth is a tiny circular aperture, the lips being sealed laterally. In spite of this still embryonic stage of development, the young manages to attach itself to the nipple of one of the two mammary glands, where it remains firmly attached for the first 6 to 10 weeks of its life. The firmness of attachment is primarily due to suction, and the nipple becomes tightly sealed into the lips by mucus

The common brush-tail phalanger, or Australian opossum (Trichosurus vulpecula).

and dried milk. Furthermore, the tip of the nipple swells inside the buccal cavity of the young, "buttoning" it to the mother. It is nevertheless possible to remove even a very small embryo only a few days old from the nipple without causing damage to either mother or young, by gently opening its mouth with a pointed matchstick and slowly pulling it off the nipple. After the initial period of continuous attachment, the embryo is frequently found in the pouch unattached to the nipple.

For three to four months the offspring resides exclusively in the mother's pouch, but as it gets older it spends more and more time outside the pouch. At the age of about 5 months it begins to eat some of the food given to the mother and at about 5 to 6 months it becomes too large for the mother's pouch but may still suck the elongated teat protruding into the opening of the pouch.

On the day before the intended milking the suckling was separated from the mother because very little milk could be obtained immediately, or even a few hours after removal of the young. For the process of milking the mother had to be anesthetized; 40 mg. per kilogram of body weight of thiopental (Pentothal) sodium given intravenously into an ear vein was found to be satisfactory. No untoward effects were noted after repeated thiopental sodium administration in either mother or young.

The milk was expressed from the turgid gland by manual pressure. This pressure has to be controlled, because if it is increased too greatly the thin skin covering the gland may split. The intraperitoneal administration of oxytocin is of assistance and results in the release of considerably more milk if carried out after the initial flow has ceased.

The smaller the young the less milk is obtained, and it is impossible to get more than a small drop in one milking from the mother of an offspring less than a fortnight old. Consequently most mothers of very small young (3.8 to 28 gm. body weight) had to be milked on a number of successive days until sufficient milk (1.5 to 2 ml.) for routine analysis had been obtained. These small young were not replaced in the pouch but were killed. Larger pouch young, from 58 gm. body weight, were kept away from their mother in a box lined with cotton-wool maintained at about 30 C for periods from 5 up to 20 hours. After the mother had been milked, the young was replaced in the pouch, where it became again attached to the nipple.

In some of the females this milking procedure was repeated at 3- to 20-day intervals and under this regimen the majority of the young developed satisfactorily and from 3 to 14 ml. of milk could be obtained in one milking provided that the young was separated from its mother overnight. The mother will also act as foster mother after its own offspring has reached an age where it can fend for itself. Lactation, however, ceases if a young is separated from its mother for eight days, and sometimes this occurs even earlier.

The age of young arriving at the laboratory in the mother's pouch was estimated from their weight by means of a nomogram on the growth of T. vulpecula constructed

by Lyne and Verhagen (1957). This allows the approximate determination of age (±6 days) from given dimensions, such as weight. The known age (±4 days) of young born in the laboratory when compared with their body weight agreed satisfactorily with this nomogram and accompanying growth curve.

Methods

Total solids, ash, protein, and fat were determined according to official methods adapted to small samples.

Lactose was estimated by the method of Somogyi (1945).

Calcium was determined by the method of Clark and Collip (1925), phosphorus according to the method of Fiske and Subbarow (1925), and iron by the procedure recommended by Elvehjem (1930) on an ashed sample of milk dissolved in dilute hydrochloric acid.

With the micro methods used 2 ml. of milk was sufficient to carry out the above analyses.

Total cholesterol was determined by the method of Schoenheimer and Sperry (1934).

Preparation of Solutions for Chromatography

Pooled milk was deproteinized with barium hydroxide and zinc sulfate (Somogyi, 1945) and the resultant filtrate concentrated to 1/10 of the original volume. A few drops of this filtrate were examined for sugars by paper chromatography. The bulk of the solution was treated with 9 volumes of absolute alcohol. The ensuing precipitate was centrifuged off, redissolved in 10 volumes of water and purified by addition to a column of Bio-Deminerolit. After displacing with 0.9% sodium chloride, the resulting solution showed a single spot on the paper chromatogram. Areas corresponding to this level were cut out from the unsprayed portion of the chromatogram and extracted with water. These extracts were hydrolyzed with N/1 sulfuric acid, neutralized with barium carbonate, filtered, concentrated, and rechromatographed.

Paper chromatography for sugars was carried out in *n*-butanol-acetic acid-water (4:1:5) or water-saturated phenol, and the spots developed with aniline hydrogen phthalate.

Findings

Over 50 samples of milk were collected from 11 brush-tail phalangers. These specimens were divided into three groups—transitional, mature, and weaning milks—and usually as many as possible of the seven routine constituents (total solids, proteins, lactose, fat, ash, calcium, and phosphorus) were estimated.

Pooled milks collected over several days from individual females with young of about 22 to 65 days (including a single specimen collected 18 days after birth) represented the transitional group (Table 1). In this group the total solids increased with increasing age of the young, being 12.6% (w/w) 18 days after birth and 19.3% 65 days after birth. In contrast the protein and lactose content remained fairly constant, amounting to approximately 6% and 3% respectively. The values for fat were more irregular and fluctuated from 1.3% to 4%. The ash increased markedly between the first and subsequent specimens.

Some 46 milk specimens considered as mature were obtained from five phalangers with young of 88 to 196 days. In Table 2 the results from three phalangers are given in some detail. The range of total solids of all mature milks examined was from

TABLE 1.—*Composition of Milk from Mothers with Young 18 to 65 Days Old*

Animal No.	Volume, Ml.	Solids, %	Ash, %	Ca, %	P, %	Protein, %	Lactose, %	Fat, %	Offspring Weight, Gm.	Offspring Age, Days
790	0.18	12.6	1.04	0.120	0.080				3.8	18
785	6 *×0.3	15.3	1.20	0.268	0.144	6.8	3.4	1.4	5.0	20
797	7 *×0.3	15.0	1.17	0.279	0.106	6.6	3.0	1.3	8.7	23
786	6 *×0.4	15.9	1.28	0.283	0.156	5.9	3.3	3.8	11.5	35
799	3 *×0.5	18.0	1.18	0.300	0.141	6.3	3.1	4.0	21.5	55
798	5 *×0.5	19.3	1.20	0.236	0.168	6.0	3.3	3.5	28.0	65

* These figures refer to number of milkings on successive days.

TABLE 2.—*Composition of Milk* of Three Phalangers† with Young in Their Pouch*

	P. 769: Days 88-178 ‡ Weight 58-615g.§				P. 771: Days 112-193 ‡ Weight 129-360g.§				P. 772: Days 105-173 ‡ Weight 97-475g.§			
	No. Det.	Mean	Min.	Max.	No. Det.	Mean	Min.	Max.	No. Det.	Mean	Min.	Max.
Solids	12	22.0	20.0	27.3	9	26.0	21.7	30.3	7	25.8	20.7	29.1
Ash	12	1.49	1.30	2.13	10	1.53	1.35	1.75	8	1.72	1.47	2.10
Ca	9	0.367	0.304	0.461	9	0.383	0.317	0.497	6	0.499	0.343	0.611
P	9	0.194	0.119	0.250	9	0.221	0.176	0.289	6	0.264	0.148	0.344
Protein	6	8.3	6.1	10.7	5	8.8	6.9	10.1	7	10.4	6.9	12.3
Lactose	7	3.7	2.8	5.1	5	3.1	2.1	4.2	7	2.8	2.3	3.6
Fat	7	4.5	2.7	8.0	5	9.7	6.5	12.0	8	4.1	1.0	7.8
Undetermined components		4.0				3.0				6.8		

* Expressed in % W/W.
† P. 769, P. 771, P. 772.
‡ Age of young at beginning and end of period of observation.
§ Weight of young at beginning and end of period of observation.

19.5% to 29.1% and the mean 24.4%. The largest fraction of the total solids was protein. The mean values varied from 8.3% to 10.8% in the five animals examined. The protein content of the milk showed an upward trend until the young reached a weight of 250 to 360 gm. After this it usually began to diminish (Table 5). Lactose was the smallest organic fraction, ranging from 1.7% to 5.1%. The "lactose" content increased from 1.1 to 2.0 times after hydrolysis of the filtrate, indicating the presence of primarily nonreducing carbohydrates. Very wide variations were met with in the fat content of phalanger milk, ranging from 1.0% to 12.0%. The ash content ranged from 1.30% to 2.13%, with an over-all mean value of 1.58%. On an average calcium accounted for 24% and phosphorus for 14% of the total ash. The iron content of a pooled specimen of milk was 0.4 mg. %. The total body iron content of six young weighing from 2.5 to 22.9 gm. varied from 0.0021% to 0.0028%, with mean of 0.0024%, of wet tissue. A few samples of mature milk examined contained 50 to 60 mg. % cholesterol.

The transition from mature to weaning milk is represented in detail in Table 3. As the young fell ill, as indicated by edema, the mother's milk took on the consistency of thick cream, and all constituents determined, with the exception of lactose, showed a marked rise. Two subsequent

TABLE 3.—*Transition from Mature to Weaning Milk: Phalanger 770*

	Volume, Ml.	Solids, %	Ash, %	Ca, %	P, %	Protein, %	Lactose, %	Fat, %	Offspring Weight, Gm.	Offspring Age, Days	
Normal composition of milk	0.5 *	22.6	1.45	0.346	0.174				93	104	
	0.2 *	23.9							106	110	
	0.2 *	25.6	1.46	0.361	0.186				125	116	
	5.0 †	24.3	1.75	0.460	0.238	9.8	2.0	6.9	153	124	
	4.0 †	29.0	1.90	0.534	0.270	11.0	1.7	6.3	230	148	
Weaning milk	2.5 ‡	35.8	2.39	0.689	0.342	13.2	1.4	13.9	260	157	Young sick and dies 3 days later
	3.5 ‡	37.7	2.26	0.689	0.347	12.8	2.1	12.9			4 days after death
	4.0 ‡	42.7	2.24	0.772	0.459	15.3	1.4	16.8			8 days after death

* Milk obtained after 5 hours' separation of young from mother.
† Milk obtained after 16 to 18 hours' separation of young from mother.
‡ Composition after young in pouch fell ill and died. Note increase of all constituents with the exception of lactose.

specimens obtained after the death of the offspring presented a similar trend and in the final specimen obtained the total solids were 42.7%. The last specimen before going dry of phalanger 772 (not included in Table 2) contained 37.6% total solids, of which 14.1% was protein and 10.1% fat.

In practically all the milks examined the total solid content exceeded the figure obtained by adding together analytical values for protein, fat, lactose, and ash. On an average the amount of undetermined substances was 5 gm. in 100 gm. of mature milk.

On paper chromatography the deproteinized filtrate of pooled samples of milk showed galactose as well as lactose. A substance was isolated from the filtrate which yielded a single spot on the chromatogram which according to its position was not identical with galactose. On hydrolysis this material yielded a product which on chromatographic examination was found to be galactose. No glucose could be detected in the hydrolysate; therefore the observed galactose could not have been derived from lactose or a polymer of lactose (Gross and Bolliger, 1958).

Comment

In contrast to that of Didelphys virginiana, the exact period of gestation of T. vulpecula has not yet been determined with certainty because phalangers seem to be reluctant to copulate in the presence of observers and are also very secretive about the birth of their single offspring. A period of gestation of about 16 days suggested by Bolliger and Carrodus (1940) is in all probability incorrect. In a recent experiment it took 20 days for young to appear in the pouch of its mother after a definitely observed copulation. This agrees with a similar observation by Lyne and Verhagen (1957), who suggested a gestation period of about 20 days.

No quantitative observations could be made on the very scanty mammary secretion during the first two weeks after birth. Milks obtained subsequently, between two and a half and nine weeks after birth, were referred to arbitrarily as transitional in analogy with the nomenclature used in higher mammals. Those obtained more than nine weeks after birth were considered mature. The transitional milk of the early postnatal period of about two and a half to five weeks and to a slighter degree up to 9 weeks was more dilute than the mature milk secreted by females with older young.

TABLE 4.—*Average Percentage Composition of Mature Phalanger, Cow, and Human Milk*

	Phalanger, %	Cow, %	Human, %
Total solids	24.5	12.8	12.4
Ash	1.88	0.71	0.21
Calcium	0.416	0.126	0.034
Phosphorus	0.226	0.099	0.015
Protein	9.2	3.3	1.1
Fat	6.1	3.8	3.8
Lactose	3.2	4.8	7.0

The total solid content of milks secreted after the period of transition up to weaning was found to be high and fairly constant in five females repeatedly examined, averaging about 25%. Compared with human or even with cow's milk one is impressed by the high protein content of the milk of the phalanger (Table 4). However, similarly high protein content is met with in the milk of some higher mammals, such as the rabbit.

The wide variations in the fat content of milk even from the same animal (1% to 12%) is difficult to explain, but it may be remembered that, for example, in cow's milk one may find a fat content of about 2% at the beginning of milking, which may increase up to about 12% at the end of milking (Whittlestone, 1954). Similar conditions prevail in human milk, as indicated by an exceptionally wide variation in fat content of different specimens (Macy, Kelly, and Sloan, 1953).

Of all the constituents examined routinely, lactose was found to be the most stable, though small in amount compared with human milk (Table 4).

In another marsupial, the kangaroo, the lactose content of the milk was found to be even smaller than in T. vulpecula (Bol-

liger and Pascoe, 1953). It is noteworthy that phalanger milk contains about five times as much cholesterol as cow's milk and three times as much as human milk.

In general the iron content of the milk is apparently sufficient for the demands of the growing suckling, because the iron content of the total body substance of the offspring between the 1st and 10th week remained stationary, indicating no depletion of the iron reserves. It may also be pointed out that for at least three months the young is completely enclosed in the pouch, and it seems that excretory products are mainly reabsorbed through the lining of the pouch of the mother, or through the thin skin of the hairless young. This arrangement may constitute, *i.a.*, an iron-conserving device.

The composition of phalanger milk resembles that of the kangaroo (Bolliger and Pascoe, 1953). The anesthetic used for milking the kangaroo was ether. On account of this interference or for other reasons the mother refused to readmit the offspring to the nipple and pouch and only one or a few specimens became available from each mother. However, as with Trichosurus there was a marked concentration in weaning milk.

Analytical values of milk of any mammal depend on factors such as age, breed, parity, diet, individual genetic factors, and procedures of collecting and preservation. For example, total solids of mature normal cow's milk, usually assumed to be 13%, may actually vary from 8.5% to 19.6% (Macy, Kelly, and Sloan, 1953). It is therefore not surprising to find variations in the composition of the milk of T. vulpecula as compared with that of higher mammals with their wide species variations. There is, however, a considerable margin of undetermined compounds, and it was felt that fundamental differences might be more in the qualitative than in the quantitative field. One instance is the presence of considerable amounts of free galactose in phalanger milk. The values given for lactose in marsupial milk therefore include that of galactose, while lactose is generally assumed to be the only sugar present in the milk of higher mammals. A further carbohydrate, foreign to Eutheria, was observed in the milk of T. vulpecula. It consisted of galactose units and has been tentatively classed as a galactan (Gross and Bolliger, 1958).

Composition of Milk in Relation to the Growth of the Young

Marsupials are born in an early embryonic stage, and the rate of growth of the pouch embryo is comparable to that of the fetus of a higher mammal and the birth weight increases about 800 times in 120 days. There is, however, in the first and to a less extent in the second month a postpartum period of comparatively slow growth as shown by the parabolic nature of the growth curve (Lyne and Verhagen, 1957). During this initial period of about 60 days the milk secreted by the mother is more dilute (transitional milk) than that secreted later on (mature milk). This change from dilute to more concentrated milk is progressive, and the beginning of near or fully mature milk secretion seems to coincide with the beginning of faster growth and also roughly with the termination of permanent attachment to the nipple.

The total solid content of mature milks was found to be high and fairly constant by Eutherian standards. Furthermore, compared with human or even with cow's milk (Table 4) one is impressed by the high protein content of phalangers' milk, which is about 6% to 7% in the first two months of pouch existence. Then, in agreement with the vigorous growth of the young the protein content of the milk increases till the offspring weighs about 350 gm. This corresponds to an age of about 4-5 months, when the young ceases to be dependent on the milk of the mother. The then ensuing decrease in protein content may help to induce the young to take solid food. With

TABLE 5.—*Composite Table Comparing the Protein Content of Mother's Milk with Body Weight of Young*

Weight of Offspring, Gm.	Protein Content of Mother's Milk, Gm. %
5.0	6.8
5.7	6.6
11.5	5.9
21.5	6.3
122	7.2
164	8.5
184	6.9
200	8.8
230	11.0
233	10.7
253	12.0
260	(13.2)
289	12.1
363	12.3
400	7.8
428	9.5
432	12.1
480	9.9
527	(14.1)
530	8.2
550	6.9
562	6.1
770	8.1
860	9.4

Note increase of protein content of mature milk with increasing body weight of offspring, followed by a decline after reaching 360 gm.

Figures in parentheses refer to weaning milk.

weaning imminent, a second rise in protein content is sometimes noted. This in all probability is secondary to the general concentration of the mammary secretion in its final stages.

No relationship to growth of the young could be observed in the fat or in the so-called lactose content of the mother's milk. Owing to the smallness of the milk sample obtainable, it was not possible at this stage to execute quantitative analyses of the observed galactose and galactan content and to relate them to an approximate age. Only pooled specimens obtained from animals of varying age were examined.

Recently E. C. Dunham (1957) has pointed out that the study of the milk of marsupials whose young are born in an early embryonic stage of development may in some way throw light on the still controversial problem of suitable feeding for the premature infant at different stages of development. The present investigation, dealing as it does mainly with quantitative estimations of conventional constituents, probably has not revealed any new facts which could be applied to the feeding of premature infants. It has, however, revealed the presence of substances not found in the milk of Eutheria, and further investigations will be directed toward a search for other substances typical of marsupial milk. These may represent special nutritional requirements of the embryo-like Metatherian offspring and thus throw some light on marsupial physiology in addition to some possible hints on the feeding of immature babies.

However, certain anatomical factors must not be overlooked when studying the feeding of the frail pouch young in its early embryonic stage of development. It is almost completely enclosed in the warm, moist pouch which acts as a natural humidicrib.

The nipple of the maternal mammary gland protruding into the pharynx of the offspring is tightly sealed in its lips, thus avoiding loss of nourishment or the sucking in of air. Furthermore, the well-developed compressor mammae, that typically Metatherian muscle of the female and analogue of the cremaster in males, may well pump milk into the young if suction should not be adequate to the demands for food.

Summary

Some 50 specimens of milk obtained from 11 parous brush-tail phalangers (Trichosurus vulpecula, a species of diprotodont marsupial) were examined for total solids, protein, fat, lactose, ash, calcium, and phosphorus.

In mature milks the quantities of constituents determined are comparable with those of concentrated milk produced by Eutheria. On an average, total solids were 24.5%, protein 9.2%, fat 6.1%, and lactose 3.2%.

The total solid content varied somewhat with the growth of the young, being less in

the first two postnatal months compared with the subsequent three to four months. It increased further in the weaning period. The initially high protein content continued to increase until the young began to take solid food.

The total body iron content of the young was satisfactorily maintained by the iron content of the milk.

Paper chromatography indicated, besides lactose, the presence of galactose as well as of carbohydrate composed of galactose units.

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Case Reports

Untoward Reaction to a New Ceruminolytic Agent

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The recent pediatric and otolaryngologic literature contains articles dealing with the use of a new ceruminolytic agent, Cerumenex,* to facilitate examination of the tympanic membranes in cases where the ear canals are occluded with wax.[1,2] The use of this agent in 40 cases in one series and in 230 cases in another was not attended by adverse side-effects.

Report of a recent unfavorable reaction, believed to be due to the use of this medication, therefore seems indicated.

Report of Case

The patient was a 2 11/12-year-old white boy. Previously the boy had had several bouts of otitis media, one of which had required a myringotomy. Also in the past there had been several episodes of bronchitis, on occasion associated with wheezing. Because of the associated wheezing, an allergic component in the boy's problem was suspected. At that time, 14 months prior to the present difficulties, cow's milk had been removed from his diet, with substitution of a soy-bean preparation. This dietary alteration proved to be helpful in decreasing the frequency of respiratory problems.

The presenting problem on June 20, 1959, was a respiratory infection with cough and wheezing, of one week's duration. Physical examination at that time revealed widespread rhonchi and some wheezing in the lungs. The pharynx had no exudate or edema, but a prominent postnasal discharge was present. A blepharitis involving the left upper lid was present. Both ear canals were occluded with wax.

Oral penicillin G in a dosage of 200,000 units every six hours, was started. He was given an injection of 0.1 cc. of an aqueous suspension of epinephrine 1:200 (Sus-Phrine), and an orally administered nasal decongestant (Triaminic) in a dosage of 5.0 cc. three times daily, was ordered. It was recommended that the mother instill Cerumenex into the ear canals each night, using cotton plugs to hold the agent in the canals.

Two days later the child was returned with the complaint of swelling and pruritus of the ears and drainage of a thin material from the ears. At that time the auricles were found to be markedly swollen and erythematous, with a small amount of foul-smelling drainage from the canals. An oral sulfaethidole preparation (Sul-Spansion), 0.65 gm. every 12 hours, was started at that time, and the ears were to be compressed with aluminum acetate solution (Burow's solution). By the following day there was swelling and erythema over the face in the region of the ears as well as the upper portions of the neck. At that time he was hospitalized at the San Mateo Community Hospital. Culture of the drainage from the ears revealed a coagulase-positive Staphylococcus aureus. He was treated with orally administered chloromycetin and erythromycin for the next six days while hospitalized. At that time there was significant diminution in the swelling of the ears and the amount of drainage, and he was discharged from the hospital to continue on the oral antibiotic medications at home for the next five days.

One month later, on July 21, 1959, when he was seen for an unrelated problem, it was discovered that the ear canals were again completely occluded with wax. Because a reevaluation of the tympanic membranes was desired, and because the previous occurrence of swelling of the ears had not been suspected to have been caused by the Cerumenex, but instead had been considered to be an external otitis secondary to the drainage from an otitis media, the use of Cerumenex was again advised. On this occasion, within several hours after the instillation of the drug in the ear canals, the auricles again became markedly swollen and pruritic, but less erythematous than on the previous occasion. At this time the cerumen and Cerumenex were removed from the ear canals by irrigation with water. The tympanic membranes were not perforated, but had a dull, gray appearance. The mother was advised not to use the

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*Cerumenex, distributed by the Purdue-Frederick Co., New York.

Cerumenex again. An ointment containing neomycin and prednisolone (Neo-Delta-Cortef) was then applied to the ear canals three times daily. Novobiocin (Albamycin) 125 mg. orally every six hours, was used for the next two days, to prevent secondary infection, as had apparently occurred on the previous occasion. By the following day the swelling of the auricles had decreased markedly, and no drainage from the ears occurred.

The occurrence of two separate episodes of sudden swelling of the auricles, each episode beginning shortly after the instillation of Cerumenex into the ear canals, and not seen in this patient at other times, constitutes presumptive evidence of a sensitivity reaction to this medication. The existence of other allergies in this patient may have been a contributing factor.

It would seem that unfavorable reactions to this drug are not as infrequent as the initial reports on it would indicate. Since the above-reported incident, I have learned of several other unexpected reactions, presumably due to the use of the drug.[3] These reactions were of the same type as this one, that is, moderate to marked swelling of the auricles.

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Two Cases of Salicylate Intoxication Successfully Treated by Exchange Transfusion

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In the past few years, the artificial kidney and exchange transfusion have been advised for removal of excessive salicylate from the body. Two cases of salicylate poisoning treated successfully by exchange transfusion are presented to show that this technique is practical and effective. A brief review of the literature is included with special emphasis on the role of hemodialysis or exchange transfusion in the treatment of salicylate and other exogenous intoxications.

Incidence of Intoxication

Summaries published by various poison control centers throughout the United States have indicated that acetylsalicylic acid is responsible for more poison cases treated in hospital emergency rooms than any other single substance.[1] A recent one-year survey of accidental poisoning in Connecticut showed that out of 322 poison cases, 33% involved acetylsalicylic acid.[2] Of 486 accidental poisonings treated in the emergency clinic of the Children's Medical Center in Boston in the two-year period 1956-1957, 146 (30%) were from the ingestion of salicylates.[3] In the Chicago Poison Center 84 of their first 500 cases involved salicylates and 73 of these salicylate poisonings resulted from flavored children's aspirin.[4] Mortality under 5 years of age is said to be 25 times greater than in any other age group.[5] Salicylates have been responsible for 541 fatalities or 7.7% of the total deaths due to accidental poisoning in the United States in the years 1952-1956. Of these deaths 380 were in children below 5 years of age.[6] From 1950 to 1957 there have been 6 deaths from salicylates in Connecticut (3 adults and 3 children).[7]

Infants are particularly susceptible to salicylate poisoning. Reilly and Worley[8] studied 42 children with salicylate poisoning and found that toxicity is particularly likely in infants on therapeutic doses, while the toddler is more prone to accidental ingestion. Heymann and Javett[9] reported 7 deaths of 15 admissions to a Children's Hospital for salicylate intoxication in 1951 alone. These were all due to therapeutic administration. More recently, Segar and Holliday[10] reported 49 cases of salicylate intoxication in children, with 5 deaths under age 2 years—also due to misguided salicylate therapy.

The lethal dose of acetylsalicylic acid is not known, but deaths have been reported from the ingestion of only 2 gm. (30 grains).[11] An adult may tolerate 15 to 30 gm.[12]

Oil of wintergreen is particularly dangerous because it is prepared in a pleasant-smelling liquid containing 90% methyl salicylate. Approximately 40% to 60% of the reported ingestions of the drug are fatal. The lethal dose is estimated at 4 to 8 cc.[13] One teaspoonful, or 4 cc., is equivalent to 2.7 gm. of acetylsalicylic acid.[3]

Report of Cases

CASE 1.—A 2-year-old white boy swallowed approximately 50 acetylsalicylic acid tablets of 0.3 gm. (5 grains) each between 9:30 and 11:00 a. m. Sunday, April 20, 1958, and arrived at the Emergency Room of Hartford Hospital at 11:30 a. m.

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TABLE 1.—*Case 1*

	Before Exchange			Exchange			After Exchange		
Hr. after ingestion	4	6	9	11.5 to 17.5		21	29	45	69
Salicylate (mg. %)	73	75	79	71	51	48	39	25	6
CO_2 (mEq/L)		15	11.5	23	21			23	
Na (mEq/L)				139	141			138	
K (mEq/L)				3.4	2.12			3.0	
Cl (mEq/L)				100	102			105	
BUN (mg. %)								7	
Hematocrit (%)	33							30	40
Sugar	158								

He had had a mild diarrhea and a general malaise for approximately 36 hours prior to admission, for which he received 6 to 8 doses of 105 mg. of acetylsalicylic acid and 2 cc. of camphorated opium tincture (paregoric) every 4 to 6 hours. He weighed 25 lb. The total amount of salicylate ingested was about 15.7 gm., or 1.42 gm. per kilogram—of which 1.37 gm. per kilogram was taken in the two hours prior to admission. Emesis was induced at home and was productive of small chunks of acetylsalicylic acid. There was no other significant past history. Gastric lavage, with approximately 1 liter of isotonic saline, was performed on arrival. Admission physical examination revealed a crying, irritable, sweating, flushed, fairly well oriented child. His temperature was 100, pulse 160, and blood pressure 90/60. Deep tendon reflexes were symmetrically hyperactive without clonus. Sensation was grossly normal, and the child was generally tremulous.

During the next four hours, symptoms progressed rapidly. The pulse rose to 200, respirations to 80, and the blood pressure stabilized at 90/40. The child was extremely thirsty, taking—and subsequently vomiting—several hundred cubic centimeters of clear liquid. Once, coffee-ground material was vomited. There was pallor at rest and cyanosis during vomiting as well as involuntary shaking and profuse sweating. From 5:30 to 10:30 p. m., his condition continued to deteriorate. He became disoriented, thrashed about in bed, and had circumoral cyanosis. He vomited all oral feedings and passed one dark-brown watery stool. The salicylate level of the plasma at 3 p.m., approximately four hours after ingestion, was 73 mg. %.* At 5 p. m., the salicylate level was 75 mg. %, and the CO_2-combining power was 15 mEq. per liter. By 8 p. m., these values were 79 mg. % and 11.5 mEq. per liter respectively. Infusion of 1,000 cc. of 5% dextrose and water was begun at 1:30 p. m. and 400 cc. of ⅙ M. sodium lactate was added at 4:30 p. m., five and one-half hours after ingestion. At 8 p. m., vitamin C, 100 mg., and vitamin K, 10 mg., were added. About 7 p. m., the Boston Poison Center of the Children's Medical Center was consulted and advised exchange transfusion. At 9:30 p. m., an exchange transfusion was started through a No. 20 polyethylene catheter, which was introduced through a No. 15 needle and was inserted into the femoral vein 3 in. In four and a half hours, approximately 700 cc. of whole blood was exchanged. The catheter was inadvertently pulled out. A cutdown onto the saphenofemoral junction was performed and a No. 18 polyethylene catheter was introduced into the saphenous vein and threaded up into the internal iliac vein.† In the next two hours 585 cc. was exchanged. A total of 1,210 cc. of whole blood was removed and 1,285 cc. of whole blood was replaced.

The patient's condition at the beginning of the exchange was fair. Respirations were 80 per minute. He was restless, disoriented, hyperreactive, crying, and sweating. During the early stages of the exchange he had periods of alternating pallor and cyanosis, increasing tachycardia and tachypnea. At one point, he appeared to be having hallucinations—staring into space and talking about balloons and ice cream cones. After 1 a. m., 14 hours after the ingestion and after the exchange transfusion was concluded, he was sleeping, but could be easily aroused. The respirations were 34 per minute, the pulse was 140 per minute, and the temperature was 101.6 F rectally. The skin was moist, but not drenched. He slept most of the day and took and retained oral feedings. He was oriented and fussy. Respirations and pulse remained approximately 35 per minute and 120 per minute respectively. The following day, he was alert, talking, and playing spontaneously. Vital signs were normal. The hematocrit reading after the exchange transfusion was 31, and he appeared

* The details of a fairly simple method for determination of plasma salicylate will be found in Reference 14.

† The exchange was technically very much easier through the larger catheter in the iliac vein. The cutdown was obtained in less than 10 minutes. We feel that this is the route of choice in this age group.

TABLE 2.—*Case 2*

	Before Exchange	Exchange		After Exchange		
Hr. after ingestion	4.5	11 to 15	19	25.5	43	67
Salicylate (mg. %)	69		38.6	32.3	17	0
CO_2 (mEq/L)	15		25	23		22
Na (mEq/L)			138			141
K (mEq/L)			3.1		3.6	4.3
Cl (mEq/L)			102			
Hematocrit (%)	39					

overhydrated. On the second day, he was given 200 cc. of whole blood, and the following morning the hematocrit was 40. He was discharged home on the third day with no complications. He returned for follow-up visit to the clinic on June 11, 1958, at which time he was entirely normal.

CASE 2.—A 3-year-old white boy weighing 31½ lbs. ingested 60 ml. of methyl salicylate (wintergreen oil) on Nov. 25, 1958, at 1 p. m. The child vomited spontaneously 15 minutes later. The mother gave a salt and water mixture on advice of her physician, and the child continued to vomit about every half hour until seen in the Emergency Room of the Hartford Hospital four and one-half hours after ingestion. At this time his temperature was 98 F, pulse 140, respirations 32, and blood pressure 110/60. The child presented with flushed facies, lethargy, and dehydration. The deep tendon reflexes were equal and 4+ bilaterally. A salicylate level at this time was 69 mg. %; the CO_2-combining power was 15 mEq/L, and the urine showed 4+ acetone. A mixture of 250 cc. of isotonic saline and 1,000 cc. of 5% dextrose was started at this time. A left saphenous vein cutdown was found unsatisfactory for exchange purposes. Therefore a cutdown on the right saphenofemoral vein junction was done, and a No. 20 polyethylene catheter was inserted into the iliac vein. Whole blood, 800 cc., was exchanged by 20 cc. units. The child became almost comatose during the procedure. Vital signs at this time were temperature 99.4 F, pulse 140, respirations 24, and blood pressure 96/50. The following morning, 19 hours after ingestion, the patient was more alert, and respirations were 26 and not as deep as previously. The serum values at this time were salicylate 38.6 mg. %, Na 138 mEq/L, K 3.1 mEq/L, Cl 102 mEq/L, and CO_2-combining power 25 mEq/L. At 2 p. m., 25½ hours after the ingestion, the salicylate level was 32.3 mg. % and the CO_2-combining power 23 mEq/L. The child received a mixture of 1,000 cc. of 5% dextrose, 750 cc. of isotonic saline, 20 mEq. of K, and 600,000 units of penicillin by intravenous infusion the second day. Oral fluids were attempted but discontinued because of vomiting. The third day the child was clinically more alert and retained fluids. Salicylate level was 17 mg. %, K 3.6 mEq/L. Oral fluids were supplemented by a mixture of 750 cc. 5% dextrose, 250 cc. of isotonic saline, and 20 mEq. of K. On the fourth day the salicylate level was 0, the Na 141 mEq/L, K 4.3 mEq/L, and the CO_2-combining power 22 mEq/L. The patient appeared recovered, and the cutdown was removed. The child was discharged on the sixth hospital day. Intramuscular procaine penicillin was given as 300,000 units b. i. d. during the last four days of hospitalization prophylactically because of two cutdown sites, although one was used only eight hours. A follow-up report in February, 1959, showed the child to be completely well.

Pharmacology and Toxicity

After ingestion, salicylates are rapidly distributed throughout the body. About 50% is excreted in the first 24 hours, traces remaining for two to three days; 70% is excreted in the urine; 20% is oxidized in the tissues, and a small amount is lost in perspiration. Acid-base disturbances are discussed in detail by other authors.[8,13,15,16] Briefly, there is an initial direct action of the salicylate on the respiratory center which leads to hyperventilation. During this stage of respiratory alkalosis, the plasma CO_2 falls and the blood pH rises. Base is excreted, causing an alkaline urine. In severe intoxications, a metabolic acidosis may develop at varying times. With acidosis, the buffer base, CO_2 content, and pH of the blood are reduced. Dehydration, if present, aggravates the situation. Hyperglycemia and ketosis may occur and are attributed to alterations of carbohydrate metabolism. Acid metabolites accumulate. Acetonuria and an acid urine may be found. Another effect of salicylate is hypoprothrombinemia, probably due to interference of the utilization of vitamin K in the liver.[17-19] Antipyrexia and resulting diaphoresis are produced by a direct effect on the thermal regulating center. Agranulocytosis and thrombocytopenia are rare complications.[16,17] Salicylates also have steroid-like effects, which may be mediated through the pituitary-adrenal axis. Some of the actions shared in common with those of corticotropin (ACTH) and cortisone

include (1) a fall in adrenal ascorbic acid and cholesterol content in experimental animals; (2) a drop in circulating eosinophils; (3) an increase in plasma hydroxycorticosteroids, and (4) increase in urinary 17-ketosteroids and uric acid excretions. They also share anti-inflammatory and antipyretic effects with the corticoids. In animals, they afford protection against anaphylactic shock.[18-20] Plasma 17-hydroxycorticosteroids have been measured in both adults and children with salicylate intoxication and found to be significantly elevated.[21] Recently hypernatremia has been described in some cases, and its possible significance is discussed in detail elsewhere.[10]

Symptoms

Symptoms of salicylism may be mild or dramatic. Vomiting usually occurs one to three hours after ingestion and is probably due both to a direct gastric irritation and to a central stimulating effect. Hyperpnea, the most classic symptom, usually begins within three to eight hours. It is of the Kussmaul type and is often misdiagnosed as diabetic acidosis.[22] Many patients have a high fever and perspire profusely. Initially, salicylates cause central nervous system stimulation, with excitement, disorientation, and increased muscular activity. Later, in severe cases, there is a central nervous system depression resulting in stupor with circulatory and respiratory failure. Hemorrhagic phenomena may occur. In fatal cases, autopsy shows bleeding throughout the body, especially in the brain. There is cerebral edema and a severe cloudy swelling in the cells of the liver, kidney, and heart.[17]

Treatment

As soon as possible, gastric lavage is indicated in any case which is seen before the stage of hyperventilation, as the absorption rate from the stomach is slow. Sodium bicarbonate should not be used in the lavage solution because it enhances the absorption of salicylates.[23] After the lavage, intravenous fluids should be administered. If the general clinical picture suggests acidosis, an alkaline solution, such as M/6 sodium lactate or 2% sodium bicarbonate, should be used. A low blood pH indicates the beginning of the acidotic phase. If pH determinations are not available, alkalinization should be started six to eight hours after ingestion. Vitamin K should be given in a dose of 1 mg. for every gram of salicylate ingested. Vitamin C is also recommended.[7-9] If convulsions are impending or occur, oxygen is indicated. Barbiturates are probably contraindicated.[24]

In severe cases, hemodialysis or exchange transfusion may be lifesaving. Indications for more radical therapy are difficult to specify. Sensitivity to the drug is variable. There is no one lethal level for all individuals. Reilly reports five deaths occurring in patients with maximum salicylate levels from 20 to 45 mg. per 100 ml.[8] In contrast, Erlanson et al. reported a 2-year-old patient who ingested 175 grains (11.7 gm.) of acetylsalicylic acid, whose salicylate level reached 73 mg. %, and yet he recovered completely.[25] The levels of Heymann's[9] six fatal cases varied from 33 to 44 mg. per 100 ml. The plasma level prior to exchange transfusion in the seven cases of salicylism in Table 3 varied from 27.5 to 160 mg. per 100 ml. All children were extremely toxic. In infants the lethal level is probably much lower than in older children and adults. A search of the literature gives us the impression that a level of over 40 mg. per 100 ml. is reason to consider exchange transfusion. Final decision must be individualized according to severity of symptoms and salicylate blood level. It is a mistake to assume that death occurs when the salicylate level is at its peak and that the danger is passed when the blood level is falling. Death may come two to three days after ingestion, and, no doubt, the persistent effect of high concentration in the tissue is as important as the height to which the blood level rises.

Exchange transfusion and hemodialysis employing the artificial kidney have been used successfully in adults and children.

TABLE 3.—*Exogenous Poisons Treated with Exchange Transfusion*

Author	Poison	Age	Weight	Amount Ingested	Blood Level Before Exch.	Blood Level After Exch.	Route	Blood Exchd., Cc.
Rentsch, Bradley and Marsh (1958)	Acetylsalicylic acid	2 yr.	25 lb.	250 grains (15.7 gm.)	79 mg. % salicylate	51 mg. % salicylate	Femoral cutdown	1,285
Bruton (1956)	Acetylsalicylic acid	28 mo.	Not stated	Over 60 grains (4 gm.)	160 mg. % salicylate	24.3 mg. % salicylate	Femoral cutdown	1,000
Radebaugh and Emery (1957)	Acetylsalicylic acid	2 yr.	Not stated	Not stated	39.8 mg. % salicylate	26.5 mg. % salicylate	Femoral cutdown	500
Heymann, Javett, and Rudolph (1954)	Acetylsalicylic acid	11 mo.	17 lb.	50 grains (3.3 gm.)	53 mg. % salicylate	28 mg. % salicylate	Not stated	1,500
Rentsch, Bradley, and Marsh (1958)	Methyl salicylate	3 yr.	31 ½ lb.	60 ml.	69 mg. % salicylate	38.6 mg. % salicylate	Femoral cutdown	800
Adams, Bigler, and Green (1957)	Methyl salicylate	20 mo.	30 ½ lb.	About 5 ml.	72.7 mg. % salicylate	41.8 mg. % salicylate	Femoral cutdown	2,035
Done and Otterness (1956)	Methyl salicylate	2 yr.	Not stated	60 ml.	86 mg. % salicylate	51 mg. % salicylate	Femoral cutdown	1,345
Katz and Carver (1956)	Isoniazid	19 mo.	24 lb.	900 mg.	38.6μg/ml/1 ml. isoniazid	26.4μg/ml. isoniazid	Radial saphenous	1,100
Boggs and Anrode (1955)	Boric acid	12 days	6 lb. 9 oz.	17 gm.	21.5 mg. % boric acid	6.9 mg. % boric acid	Umbilical	1,040+ 570
Bruton (1956)	Pentobarbital	2 yr.	Not stated	1,700 to 1,000 mg.	Not stated	Not stated	Femoral cutdown	2,290
Bruton (1956)	Pyridium	3 yr.	Not stated	Unknown	40 gm/100 ml. methemoglobin	Not done	Femoral cutdown	1,000

Both methods will effectively lower serum salicylate levels.[9,12,13,26-28] In 1951, Doolan et al. reported a 39-year-old man who took over 40 gm. of acetylsalicylic acid. During one hour of dialysis, 1,300 mg. of salicylate was removed.[12] Schreiner, in 1955, reported a 44-year-old patient in coma who was dialyzed for six hours, lowering the salicylate level from 91 to 34 mg. per 100 ml.[29]

We found only nine detailed case reports of the use of exchange transfusion in the treatment of exogenous intoxication in the English literature. Five of these were for salicylate poisoning and four for other drugs. All the patients survived. In 1954, Heymann et al. were the first to report a successful exchange transfusion for poisoning in an 11-month-old infant who ingested 50 grains (3 gm.) of acetylsalicylic acid over a three-day period. Whole blood, 1,500 cc., was used to lower the salicylate level from 53 to 28 mg. %.[9] Another case of acetylsalicylic acid poisoning was a 2-year-old reported by Radebaugh et al. in 1957. The amount ingested was unknown. The salicylate level was 39.8 mg. %, and the child was moribund. Since they had experienced two fatalities with salicylate levels in the range of 40 mg. %, an exchange transfusion of 500 cc. of blood by the femoral cutdown route was performed. The level dropped to 26.5 mg. %, and the child became responsive. No further transfusions were necessary.[27] Recently, in 1958, Bruton[28] reported a case of a 28-month-old child who ingested over 60 grains (4 gm.) of acetylsalicylic acid. The blood level was 73 mg. % just two and one-half hours after ingestion. At four hours after ingestion it was 121 mg. % and at six hours it was 160 mg. %! Immediately after an exchange transfusion of 1,000 ml. of blood via a femoral cutdown, the level dropped to 24.3 mg. %.

Two cases of methyl salicylate intoxication were reported. Done et al.,[26] in 1956, reported a 2-year-old who ingested 60 ml. of wintergreen oil. An exchange of 1,345 cc. of blood by way of a femoral cutdown was performed, lowering the salicylate level from 86 to 51 mg. %. Adams et al.[13] reported a 20-month-old infant who ingested 5 ml. of wintergreen oil. A salicylate level of 72.7 mg. % was lowered to 41.8 mg. % by the exchange of 2,035 cc. of blood through a femoral cutdown.

The exchange transfusion has been useful for poisons other than salicylates. In 1955, Boggs[30] treated a 12-day-old infant who ingested 17 gm. of boric acid powder by an exchange transfusion of 1,040 cc. of whole blood through an umbilical vein. Twenty-four hours later, a repeat exchange of 570 cc. of blood was performed. Katz et al.[31] in 1956 performed an exchange transfusion in a 19-month-old baby who ingested 900 mg. of isoniazid (INH). They exchanged 1,100 cc. by the radial artery-saphenous vein method. Bruton reported a 2-year-old who ingested 1,700 to 1,000 mg. % of pentobarbital (Nembutal) and responded after an exchange transfusion of 2,290 cc. of blood via a femoral cutdown. The same author reported a 3-year-old who ingested an unknown quantity of phenylazodiamino-pyridine hydrochloride (Pyridium) and whose methemoglobin level was 40 gm. per 100 ml. before 1,000 cc. of blood was exchanged through a femoral cutdown. All of these patients survived and did well.

The French have extensively used exchange transfusions. Details of their cases are not available in the English literature; however, there are several good review articles.[32,33] In 1949, Bessis reported over 190 exchange transfusions in children and adults. These were for erythroblastosis fetalis, intoxications, acute renal failure, and acute leukemia.[32] No case of the use in salicylate intoxication is specifically cited.

It is difficult to compare the merits of exchange transfusion as opposed to hemodialysis. Exchange transfusion requires fairly massive amounts of blood and carries hazards associated with multiple large blood transfusions. If anticoagulant in bank blood is a citric acid, sodium citrate complex, it will alkalinize the system. This may or may

not be advantageous. The equipment is relatively simple and is available in most general hospitals. Specific details of the technique are presented elsewhere.[32,34-37]

The artificial kidney is not universally available and must be operated by a highly experienced team. The technical problems are compounded in infants and young children. Two to three pints of blood must be used to prime the system, and therefore this method also carries the dangers associated with blood transfusions.

Summary

Two cases of severe salicylate poisoning successfully treated by exchange transfusion are presented. A discussion of the pharmacologic and toxic effects of salicylates as well as a rationale of conventional medical therapy is given. Indications for exchange transfusions or hemodialysis are discussed.

360 Griswold St.

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Ipecac Is Not Innocuous

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Ipecac syrup and ipecac fluidextract are commonly used for a variety of reasons in pediatric practice.

This brief history of the difficulties following the ingestion of ipecac fluidextract is presented as a reminder of the differences between ipecac fluidextract and ipecac syrup, and the potential toxicity of each.

A 2½-year-old child, a son of a physician, ingested approximately six 4 mg. chlorpheniramine (Chlor-Trimeton) maleate tablets. The father, a surgeon then on rounds at the local hospital, consulted with a group of three pediatricians as to what would be appropriate therapy. It was the agreed consensus that the child should be given "ipecac," a teaspoonful every five minutes until vomiting ensued. The father obtained from the local hospital pharmacy a bottle of ipecac, fluidextract, dispensed by a substitute pharmacist who was on duty for this one day only. The near catastrophe that followed points up the fact that ipecac is not innocuous.

The boy was given 15 cc. of the ipecac fluidextract over a 30-minute period. He then began to vomit and continued to do so, violently, for eight hours. He continued to vomit intermittently for two and a half days, and he developed diarrhea that became tarry (benzidine dichloride positive).

Approximately 60 hours after the initial ingestion he was admitted to the local hospital, moderately dehydrated, for intravenous fluid therapy. He continued to vomit more frequently for the next 48 hours, until a No. 30 Baxter polyethylene feeding tube was inserted and intermittent Wangensteen suction was started. The vomiting was controlled by this measure. The tube was in place for four days.

His course was complicated by (1) leukopenia and neutropenia of uncertain etiology, possibly secondary to chlorpheniramine or ipecac[1]; (2) acute fluid and electrolyte problems, leading at one point to a low-sodium state and convulsions necessitating administration of 5% Na Cl; (3) pneumonia and pleural effusion; (4) phlebitis, secondary to 5% Na Cl administration; (5) EKG changes (ST and T wave).

In spite of these complications he improved to the point where he was discharged on the 17th hospital day, able to take liquids and semisolids by mouth.

He was able to eat nonbulky foods at home for about one month. However, at that time he began to gag occasionally and to work up the bolus (sometimes only water) by a process of reverse deglutition. This was intermittent at first but became increasingly frequent, and his nutrition began to suffer.

He was readmitted to the local hospital where esophagoscopy revealed a constricted lumen with marked inflammation in the distal one-third of the esophagus. Attempts to pass the smallest tubes and instruments were unsuccessful.

A few days later by way of a gastrostomy the esophagus was dilated from below. The area of stenosis was less than 1 cm. in length.

Continuing bouginage at twice weekly intervals for one month enabled the patient to eat moderately bulky foods. However, if bouginage was not carried out, swallowing would become increasingly difficult. Currently he is being dilated with mercury-filled bougies at monthly intervals. Following bouginage his ability to take bulky foods is greatly enhanced. The state of his nutrition is now optimal.

Comment

It should be pointed out that ipecac * fluidextract is 14 times more potent than ipecac syrup in terms of primary alkaloids present (i.e., emetine and cephaeline). Emetine is thought to be the ingredient primarily responsible for toxic manifestations, although cephaeline has a more potent emetic action. Emetine constitutes more than half of the total alkaloidal content of ipecac.

Standard texts of pharmacology and toxicology[2-5] make little or no mention of poisoning due to ingestion of ipecac. However, much is written regarding emetine

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* Ipecac consists of the dried rhizome and roots of Cephaelis ipecacuanha of Cephaelis acuminata. It contains a number of alkaloids—emetine, cephaeline, and psychotrine being of primary importance.

intoxication. Goodman and Gilman list the systemic effects of emetine toxicity as follows:

1. Gastrointestinal manifestations
   (*a*) Diarrhea, which can be severe, presumably due to direct action of emetine on intestinal musculature
   (*b*) Nausea and vomiting—both probably central in origin
2. Neuromuscular
   (*a*) Weakness, aching, tenderness, and stiffness of skeletal muscles, especially of the neck and the extremities
   (*b*) Mild sensory disturbances and tremor
   (*c*) Edema may occur
3. Cardiovascular
   (*a*) Hypotension
   (*b*) Precordial pain
   (*c*) Tachycardia
   (*d*) Dyspnea
   (*e*) EKG abnormalities

The literature makes no mention of stenosing esophagitis as a direct result of ipecac or emetine ingestion. Whether the action of the ipecac fluidextract directly on the esophageal mucosa and muscle, or the prolonged vomiting with resultant acid-peptic esophagitis was responsible for the stenosis in this case, and what role the gastric tube played in this aspect of the case, if any, are matters for speculation.

Summary

A case of stenosing esophagitis is presented that followed ingestion of ipecac fluidextract. Attention is called to the differences between ipecac fluidextract and ipecac syrup, and the potential toxicity of each.

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Cerebrovascular Accidents Occurring as a Complication of Cardiac Catheterization

A Report of Two Cases

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Cardiac catheterization is an accepted diagnostic technique with a mortality of less than 0.5%[1] and a correspondingly minor postoperative morbidity. Frequently this procedure is performed on older children and adults on an outpatient basis with only meperidine (Demerol) analgesia and local procaine infiltration anesthesia.

One of the well-known potential hazards of congenital heart disease, particularly cyanotic congenital heart disease with secondary polycythemia, is the development of intracranial complications, either brain abscess[2] or spontaneous cerebral arterial thrombosis.[3] Cerebral artery thrombosis is most likely to occur during periods of dehydration or when the hematocrit is so high that the viscosity of the blood is increased appreciably.[4] The occurrence of this complication during the procedure of cardiac catheterization has not been reported. Within a period of two months, two patients, one with severe cyanotic congenital heart disease and another with an acyanotic congenital heart lesion, developed manifestations in the immediate postcatheterization period which were compatible with the diagnosis of cerebral artery thrombosis. An analysis of the unique features of these cases will be made and prophylactic measures to prevent recurrence of this problem will be suggested.

Report of Cases

CASE 1.—A 7-year-old girl with a clinical diagnosis of tetralogy of Fallot was admitted for cardiac catheterization preparatory to open-heart surgery. Cardiac catheterization had been recommended several years previously, but the mother, a practical nurse by profession, had refused consistently to have the procedure performed.

Physical examination revealed a thin, deeply cyanotic, and apprehensive 7-year-old girl whose height was 61 in. and weight 51 lb. Blood pressures were 116/60 in the right arm, 128/60 in the left leg. Pulse rate was rapid, 110, and the respiratory rate was normal. There was marked cyanosis of the ears, lips, and nailbeds, and marked clubbing of the fingers and toes. Other pertinent physical findings were limited to the heart. There was mild left precordial prominence. The P.M.I. was at the xiphoid, and there was a mild systolic forward thrust. There was a harsh Grade III systolic murmur of maximal intensity in the third left intercostal space along the left sternal border. This murmur was audible over the entire chest anteriorly, but was transmitted particularly well to the pulmonic auscultatory area and to the left clavicle. The pulmonary second sound was diminished in intensity and appeared single.

Urinalysis was normal. There was a moderate polycythemia: the hematocrit was 58% and the hemoglobin, 18.5 gm. %. With the degree of arterial blood unsaturation which this patient demonstrated during cardiac catheterization, these levels probably represented a mild relative iron-deficiency anemia,[4] which was confirmed by the finding of microcytic hypochromic red blood cells in the blood smear. Fluoroscopy demonstrated a small heart with evidence of right ventricular hypertrophy, absence of the pulmonary artery segment, and diminished pulmonary blood flow. An electrocardiogram demonstrated a tall R wave in lead V_1 with a delay in the onset of the intrinsicoid deflection, and deep S-waves in the left ventricular leads, compatible with the diagnosis of right ventricular hypertrophy.

Cardiac catheterization was performed on the second hospital day under meperidine-promethazine-(Phenergan)-chlorpromazine-(Thorazine) analgesia. The dose was 1.75 cc/20 lb. of body weight as recommended.[5] At the beginning of the catheriza-

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TABLE 1.—*Cardiac Catheterization Data of Case 1*

Hemoglobin: 15.3 gm. % Hematocrit 52.5%
Oxygen Capacity: 21.4 Vol. %

Location	Oxygen Content, Vol. %	Oximetric Reading	Pressure, Mm. Hg.
Right subclavian artery	6.28	43	—
Aorta	6.76	43	65/35
Right ventricle	4.32	39	62/0-85/0
Pulmonary artery	3.16	36	(Mean) 5 mm.
Low right atrium	2.60	34	(Mean) 4 mm.
High right atrium		34	
Superior vena cava	2.36	33	
Inferior vena cava	.66 *	30	

* This sample was taken in duplicate and run in quadruplicate, the same result being obtained each time.

tion the child seemed more deeply sedated than the other children who had received comparable doses of this medication. The catheterization was uneventful and completed within an hour's time. The results are listed in Table 1. These confirmed the clinical impression of tetralogy of Fallot. Of particular interest are (1) the low arterial oxygen content of only 6.76 Vol. % and the correspondingly low oxygen content of the blood in the other chambers of the heart; and (2) the very low arterial pressure obtained in the aorta, 65/35 mm. Hg. The pulmonary stenosis was so severe that no pressure pulse waves could be seen, and an estimate of the mean pressure had to be made from the tracings.

The patient was quiet throughout the procedure; she stirred occasionally and cried out once or twice. Four hours after the procedure she started to hyperventilate and could not be roused. For the next 12 hours this hyperventilation continued, and the patient developed hyperventilation tetany. Dehydration became apparent, and intravenous fluids were given. Her total urinary output for the 24-hour period was only 150 cc.

The following morning, 18 hours postoperatively, the patient cried in response to painful stimulation. Though cerebral artery thrombosis was suspected, no localizing signs were apparent. The patient's neck seemed slightly rigid and she cried when the neck was flexed. Later during the day signs of a hemiparesis had developed and the degree of coma had become less. The child began to suckle-feed by bottle and to consume soft foods.

The neurological consultant felt that the patient demonstrated weakness bilaterally, more marked on the left than on the right. Cranial nerve function appeared to be intact, and no facial weakness was apparent. To rule out brain abscess, spinal tap was performed. The fluid contained 20 RBC/hpf; protein, 31.0 mg. %, and sugar 51 mg. %. The consultant felt that the findings were compatible with a diagnosis of basilar artery thrombosis.

The patient's level of consciousness changed little after the second postoperative day. On the third postoperative day the mother complained that the child was getting too much attention and that her state was due to fright caused by the Medical Staff. Therefore, she signed the patient out of the hospital against medical advice. Follow-up information obtained from the referring physician states that the patient's course was one of gradual improvement to almost complete recovery with a slight residual weakness of the right leg.

CASE 2.—A 20 month-old female was admitted to the Salt Lake General Hospital for diagnostic cardiac catheterization. A heart murmur was noted first during a routine well-baby examination at 4 months of age. Physical growth and development were comparable to that of her siblings, although the child seemed to be retarded in mental development. At 20 months she sat poorly with support and could not stand. She could say one or two words and did not appear to be interested in her environment. She was hyperkinetic, and without sedation it was difficult to examine her thoroughly. She had never been cyanotic.

Physical examination revealed a nicely proportioned female infant with a height of 31 in. and a weight of 22 lb. Blood pressures were as follows: 98/70 mm. Hg. in the right arm and 110/70 mm. Hg. in the right leg. The pulse rate was 100. Other pertinent physical findings were limited to the cardiac and neurologic examinations. There was moderate precordial prominence, a xiphoid impulse, and a right ventricular thrust. Cardiac auscultation revealed a loud, harsh, systolic ejection murmur of maximal intensity in the second left intercostal space, unaccompanied by a thrill. The

TABLE 2.—*Cardiac Catheterization Data of Case 2*

Hemoglobin: 10.5 gm. % Hematocrit 34%
Oxygen Capacity: 13.9 Vol. %

Location	Oxygen Content, Vol. %	Oximetric Reading	Pressure, Mm. Hg.
Main pulmonary artery	7.2	65	15/6
High right ventricle		63.5	
Mid right ventricle	7.7	65	72/0
Low right atrium	6.8	62	10/0
Mid right atrium		59.5	
High right atrium	5.9	57	
Superior vena cava		58.5	
Inferior vena cava	5.5	52	
Pulmonary vein	12.2	98	22/5
Left atrium	11.6	95	
Left ventricle	11.6	95	85/0
Aorta			85/36
Femoral artery	11.2		

murmur was transmitted along the upper sternal border and outward toward the clavicle. The pulmonic second sound was split and markedly diminished in intensity.

The child was irritable and grossly retarded from the standpoint of mental and motor development. Babinski reflexes were positive bilaterally, but no sign of a localized abnormality were observed.

Cardiac catheterization was performed through the right greater saphenous vein under meperidine-promethazine-chlorpromazine analgesia. The procedure was prolonged, owing to difficulties encountered in the isolation of the vein and several repeated samplings in the various cardiac chambers. In addition, the laboratory was very hot, owing to a failure in the air-conditioning system. Data obtained during cardiac catheterization are listed in Table 2. A systolic gradient of 57 mm. Hg. was measured across the pulmonary valve and the catheter passed through the interatrial septal defect. Catheterization data were interpreted as demonstrating an interatrial septal defect and a mild pulmonic stenosis.

After completion of the procedure the patient's temperature rose rapidly to 105 F rectally. She was comatose and dehydrated as evidenced by dryness of the lips and mucous membranes, poor skin turgor, and anuria. Intravenous fluids were administered in the amount of 1,800 cc. per cubic meter for 24 hours. Temperature fell to normal; however, 12 hours after the procedure she still could not be aroused. No focal neurological signs could be elicited. Coma persisted through the following day, and 36 hours after the procedure there were a persistent deviation of the eyes to the left, a left facial paresis, and a right hemiparesis. A lumbar puncture was performed. Fluid dynamics were normal, but the fluid was opalescent and pink in appearance. Cell count was 11,000 R.B.C. per cubic millimeter, protein 34 mg. %, and sugar 60 mg. %. The supernatant fluid was clear. Thereafter, her sensorium gradually cleared, and three days after operation she regained almost completely the function of the right extremities. She was discharged on the sixth postoperative day with a minimal left facial weakness and a minimal weakness of the right hand.

Six weeks later the patient was admitted for surgical correction of her cardiac defects on the bypass circulation. Neurological examination demonstrated a mild left facial weakness evident only on crying. At surgery the findings of the cardiac catheterizatioı. were confirmed. Repair of a foramen-ovale type of septal defect and a Brock pulmonary valvulotomy under direct vision were performed. The patient tolerated the procedure well and was discharged on the 14th postoperative day.

Comment

Cardiac catheterization properly performed is a relatively safe diagnostic procedure. An occasional death results from ventricular fibrillation; this can be avoided usually by careful visual monitoring of the electrocardiograph during the procedure. The judicious use of sedative and analgesic agents obviates the necessity of general anesthesia in the young age group and eliminates the risk accompanying anesthesia.

The occurrence of cerebrovascular accidents during or following cardiac catheterization has not been reported. In over 900 catheterizations performed in the clinic since 1950, this difficulty had not been encountered previously. However, within a short period of time this complication was observed twice, in a child with tetralogy of Fallot with a moderate degree of secondary polycythemia and in a child with an acyanotic lesion and normal hematocrit (interatrial septal defect and mild pulmonic stenosis with a left-to-right shunt).

Two features were common to the clinical course of these patients. Both were catheterized using a combination of meperidine, promethazine, and chlorpromazine, reputedly a safe form of analgesia for this procedure, and both patients developed extreme dehydration. It was felt that the latter factor was of prime importance in the development of cerebral thrombosis in these patients. However, in Patient 1 the hypotensive effect of meperidine-promethazine-chlorpromazine could have played a contributory role. The degree of polycythemia in Case 1 was not sufficiently great to increase the viscosity of the blood to the point where spontaneous thrombosis is likely to occur.

In the second case an additional factor must be considered. This child presented objective evidence of neurological involvement in that she was developmentally retarded. In addition she had had several episodes in the past which may have been seizures.

As a result of these experiences it is suggested that careful attention be paid to the state of hydration of the patient prior to cardiac catheterization. If a prolonged procedure is anticipated, some provision should be made to supply maintenance fluid requirements. A careful record of fluid administered and blood withdrawn should be kept.

Summary

Cerebral vascular accidents, presumably cerebral thrombosis, occurred during or following cardiac catheterization in two patients. Dehydration and possibily the hypotensive effects of the meperidine-promethazine-chlorpromazine analgesia employed appeared to be the main contributory factors. Prevention of this complication by adequate fluid administration during the procedure is suggested.

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Idiopathic Hypercalcemia of Infancy

Report of a Case and a Review of the Literature

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In 1952, Lightwood and Payne [1] described a new clinical entity which they termed idiopathic hypercalcemia. It was characterized by its occurrence before the age of 1 year, by anorexia, vomiting, constipation, hypotonia, and failure to gain. Clinically it resembles a disease previously described by Lightwood,[2] infantile renal acidosis, but differs biochemically in that the former has an elevated serum calcium while the latter a hyperchloremic acidosis. Lightwood distinguishes this condition from one described by Fanconi [3] in which the children had mental retardation, chronic renal disease, osteosclerosis, increased NPN, hypertension, elevated serum calcium, and death from renal failure. As there have been some cases of intermediate severity between the two, with a course leading to death, there has been some conjecture as to whether these are related syndromes representing the extremes of a broad spectrum. With no intent to state positively that these are unrelated diseases, this article will refer to the more prevalent form as described by Lightwood.

Report of Case

The patient was born May 13, 1955, and was first seen on Feb. 9, 1956, at the age of 9 months. Weight was 15¼ lb. (7,030 gm.) (3 percentile for 7 months) and height was 28¼ in. (50 percentile for 9 months). He was referred because of failure to gain weight in the past four to five months, anorexia, poor development, recent pulmonary infection, and constipation.

His birth weight was 9 lb. 10 oz. (4,365 gm.) and at 2 weeks of age he weighed 10 lb. 4 oz. (4,650 gm.). At 8 weeks he weighed 12 lb. (5,445 gm.). The only other recorded weight, on Jan. 13, 1956, is 15 lb. 4 oz. (6,915 gm.). He was on an evaporated milk formula from birth, and this was changed to cows' milk at 5 months. He had been taking cereal, fruits, cheese, eggs, and 24-32 oz. of milk. He had been on ABDEC drops (multivitamin preparation), 0.6 cc., since birth, once daily, and one dropper of Zymatinic drops (Lematinic with vitamin supplement.)

He was said to have had a normal birth and normal development. He was free of all infection until two months before his visit, when he developed a persistent cough.

Family consists of parents and seven other children. A maternal aunt had diabetes and one child (not examined) is said to have a low I.Q., but the family states that he is not mentally retarded.

Physical examination disclosed a very sociable child who smiled readily, was unable to sit up, had a marked head lag, and a decreased amount of subcutaneous tissue. ENT was normal; coarse rhonchi and rales were heard diffusely throughout the chest. He had flaccid abdominal musculature; no organ enlargement, and no masses were palpable. He was very hypotonic, not reaching out for toys, but was alert and sociable. As the pulmonary infection persisted he was hospitalized on Feb. 21, 1956.

Laboratory results at this time showed the following: normal urine; hemoglobin 14.2 gm/100 ml.; white blood count 17,200 cu. mm.; differential count normal; nonprotein nitrogen 39 mg/100 ml.; CO_2-combining power 30 vol/100 ml.; sodium 143 mEq/L.; phosphorus 5.7 mg/100 ml.; chloride 107 mEq/L.; potassium 4.3 mEq/L.; calcium 13.9 mg/100 ml., and when repeated 14.3 mg/100 ml. Duodenal intubation revealed adequate trypsin; albumin was 5.1 gm/100 ml., and globulin was 2.8 gm/100 ml.

Chest x-ray on Feb. 13, 1957, showed pneumonitis in both cardiophrenic angles. Repeat chest x-ray on Feb. 22, showed incomplete resolution. X-rays of the paranasal sinuses were normal. X-rays of the ankles and wrists showed normal bone age with evidence of linear bands of increased density at the proximal and distal aspects of the long bones. These were thought to represent areas of arrested bone growth.

Follow-up: As the hospital work-up was consistent with idiopathic hypercalcemia, it was de-

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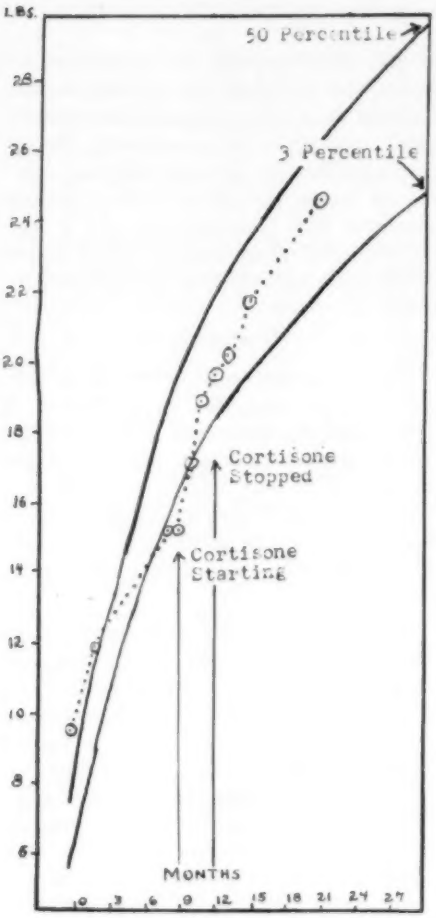

Fig. 1.—The weight curve of the patient from birth to 21 months of age.

cided to treat him with cortisone, eliminate vitamin D, place him on a low-calcium milk (Soyalac) 3.6 mg/100 cc., and avoid foods high in calcium. The clinical response was dramatic. Within one month of discharge he gained 2 lb., and he continued to gain steadily, as can be seen from Figure 1. Shortly after treatment, he began to sit up, and the hypotonia disappeared. At one year he was crawling and standing and at 14 months he was walking.

He was taken off cortisone after three months of therapy and continued to progress. He is still on a low-calcium milk diet with no vitamin D added.

Follow-up of his serum calcium showed a slow gradual decline, as can be seen from Figure 2.

Clinical Picture

The clinical picture in this disease is that of an infant who has been gaining well prior to the age of 4 to 9 months. The child may then show symptoms of anorexia, vomiting, constipation, hypotonia, and a failure to gain. A number have been described with systolic murmurs thought to be a result of valvular calcifications. Usually, the infants are happy, alert, and appear socially normal for their age but grossly retarded in physical performance. Intercurrent infections, primarily respiratory in nature, are frequent. Dehydration is present in proportion to the amount of vomiting which occurs.

The biochemical findings are specific for the disease, while the clinical findings are very nebulous and diffuse. There is a per-

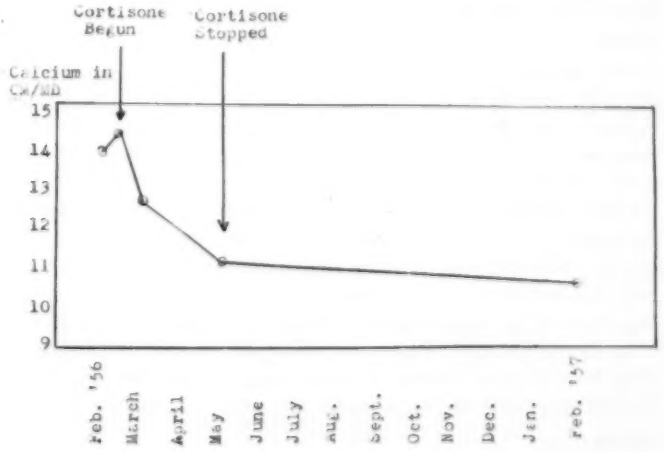

Fig. 2.—The serum calcium levels of the patient from the time he was first examined at 9 months of age until last seen at 21 months of age.

sistently high serum calcium of 12-18 mg/100 ml. The alkaline phosphatase and phosphorus are normal. The NPN is moderately elevated in most cases, the cholesterol may be elevated, and the urine may have albumin and pus cells.

There have been occasional reports[4] of an increased density of the metaphyseal margins of the lower ends of the radius and ulna. Others have reported minute calcifications in the area of the kidneys.

The course of the disease is typically benign and self-limited. It usually responds to treatment. After a variable period of treatment, normal gain of weight is induced, and the serum calcium is brought down to normal. In the cases that have responded to treatment it has been noted that they later tolerate vitamin D and normal calcium diets. Forfar[5] has shown that children who have recovered absorb calcium in normal amounts whereas previously they had absorbed calcium in excess.

Atypically, the disease can be very severe and the response to treatment very poor. These children have been described as being very dehydrated, vomiting perniciously, and sudden, unexpained death may occur. Mitchell and Rhaney[6] described three such infants and their necropsy findings. The deaths were sudden, unexplained, and the principal findings limited to the kidneys. The kidneys showed areas of interstitial and subepithelial calcifications of the medulla. There were no vascular or infectious lesions.

The mechanism of the clinical and biochemical symptoms is not entirely clear. Forfar[5] and Morgan[7] have shown that children who are clinically active demonstrate increased calcium absorption, increased urinary output of calcium, and increased intestinal absorption of phosphorus. The calcium retention, hypercalcemia, hypercalcuria, and azotemia are all suggestive of a vitamin D-like effect.

In the differential diagnosis, these children present as a failure to gain weight. Failure to gain, in an infant under one year of age, should prompt one to examine the serum calcium. When this is done, the differential diagnosis is easy. Unlike infantile renal acidosis, the CO_2 is normal. Hyperparathyroidism is ruled out because of the normal serum phosphorus. Other diseases associated with hypercalcemia such as sarcoid, immobilization, and malignant disease of the skeleton are readily distinguished.

Treatment

Positive evaluation of treatment is difficult because idiopathic hypercalcemia is self-limited. Children when actively afflicted are intolerant of a normal calcium diet and of vitamin D, but may be returned to a normal diet after they have been cured. A low calcium intake, elimination of vitamin D, and cortisone have been used in treatment.

A low-calcium diet was achieved by Ferguson,[8] who passed milk through an exchange resin, removing most of the calcium. He later prepared milk containing 2 mEq/liter of calcium from a low-ash casein. Stapelton[10] uses a low-calcium milk (Locasol) containing 50 mg. calcium/qt., which has been found to cause a negative calcium balance and to clear the clinical symptoms. The withdrawal of vitamin D supplements from the diet finds acceptance from all who have reported treating the condition. No case of rickets has been reported from any patient undergoing treatment.

Creery and Neil[9] introduced the use of small amounts (12.5 to 25 mg/day) of cortisone and reported rapid recoveries. It has been shown by Anderson,[11] Forfar,[5] Morgan,[7] and Henneman[12] that cortisone will decrease calcium absorption, increase urinary calcium, and lower the serum cholesterol. Forfar[5] demonstrated that cortisone is effective even in the presence of calciferol. Henneman[12] demonstrated that the addition of a cereal (such as All-Bran) high in phytate content may still further increase the fecal calcium by binding the calcium in the intestinal secretions.

The treatment of choice is a low-calcium diet, elimination of vitamin D, and a high phytate diet. Cortisone is reserved for those cases where a low-calcium diet is unattainable or where the patient's condition is critical.

According to Stapelton,[10] the patient may be returned to a normal diet if he has normal serum calcium, normal NPN, steady gain in weight, and a rise in the serum alkaline phosphatase.

Summary

A case of idiopathic hypercalcemia of infancy has been presented. This is a recently described disease occurring before the first year of life. It is characterized by anorexia, vomiting, failure to gain weight, and high serum calcium. Its etiology is unknown, but it clinically and biochemically resembles vitamin D overdosage. This condition is self-limited and responds to treatment. A low-calcium diet, elimination of vitamin D, and a high-phytate diet are the treatments of choice. Cortisone has been found to be very effective and is useful in severe cases.

I wish to thank Lawrence Kalom, M.D., of Zion, Ill., for referring this patient to me.

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Abstracts from Current Literature

American Heart Journal, St. Louis

Abstracted by F. Kathryn Edwards, M.D.

57, No. 5 (May) 1959

* Postpericardiotomy Syndrome in Congenital Heart Deformities. John L. Johnson.—p. 643.
* Recatheterization of the Right Heart in Ventricular Septal Defect. Daniel F. Downing.—p. 669.
Myocarditis. O. Saphir.—p. 639.
Isolated Infundibular Stenosis. S. Gilbert Blount, Phillip S. Vigoda, and Henry Swan.—p. 684.
Clinical and Physiologic Studies in Ebstein's Malformation. W. R. Livesay.—p. 701.

Postpericardiotomy Syndrome in Congenital Heart Deformities.—This author reports on 11 patients studied over a three-year period who demonstrated the postpericardiotomy syndrome following operation for congenital defects. In all cases the pericardium was opened.

The symptoms occurred either in less than 7 days or between 15 and 30 days. There was no difference in occurrence between the two sexes. The true incidence of the syndrome is unknown.

The most constant sign was fever. Generalized chest pain was present in three, and specific pain in the area of the sternum was present in two others. Pain in the left shoulder and arm occurred in three patients. Four patients had evidence of pericardial fluid. A friction rub was heard in six. Pleural fluid, unilateral and bilateral, was observed in six. A tender and/or enlarged liver was found in six patients.

The white blood count was elevated in eight patients. The x-rays showed a characteristic enlargement of the heart either at the time of development of symptoms or signs, or within one to two days. Fluoroscopy showed decreased cardiac impulse in two patients; pleural fluid was seen in seven, and pneumonitis in five.

Antibiotics did not shorten the course of the illness. The symptoms and signs disappeared in from two weeks to one month in most cases. Several patients required digitalization along with restriction of activities.

Recatheterization of the Right Heart in Ventricular Septal Defect.—Twenty patients with ventricular septal defects were recatheterized 17 months to 8 years after their initial study in order to evaluate the natural history of the disease.

Only patients with isolated ventricular septal defect were included. Ten males and ten females are included. The age of initial study ranged from 6 weeks to 13 9/12 years. The second study was done between the ages of 19 months and 17 5/12 years.

The pressure in the pulmonary artery was normal in the initial study in four patients and remained so on repeat study done 2 5/12 to 8 4/12 years later.

In the remaining 16 patients the systolic pressure in the pulmonary artery ranged from 32 to 90 mm. of Hg (35% to 100% of systemic systolic pressure). One patient had identical pressures recorded at 7 months and 3 years of age. Three patients had a rise in pulmonary systolic pressure (increasing 2%, 7%, and 11% of systemic systolic pressure).

In 10 patients there was a decrease in the ratio of pulmonary systolic pressure to systemic systolic pressure of from 2% to 44%.

During the interval between catheterizations there was no significant change in physical findings. The cardiac size and pulmonary vascular bed were not significantly changed by x-ray during the interval.

The electrocardiogram was changed in only two patients. One, an infant of 3 months, who had a pulmonary systolic pressure of 60 mm. Hg, had a significant decrease in the amplitude of the R wave in the right precordial leads 19 months later, when the systolic pressure in the pulmonary artery measured 29 mm. Hg. The other patient, aged 6 11/12 years when initially studied, had a pulmonary artery systolic pressure of 78 mm. Hg and showed right ventricle hypertrophy which changed to biventricular hypertrophy three years later. There had been an increase in the ratio of pulmonary to systemic systolic pressure of 7%.

* These articles are abstracted in this issue.

Although the series studied is small, the data obtained tend to prove that pulmonary vascular resistance, as measured by pulmonary pressure, changes little in the majority of patients over several years. A rise in pressure occurred only rarely.

The author points out that the mortality from corrective surgery for ventricular septal defect is far from negligible. Since there is little evidence of progression of the pulmonary vascular pressure over this period, surgery could be safely delayed in many patients for at least a few years.

Surgery could be logically offered to the patient whose pulmonary pressure has been demonstrated by serial catheterization to be rising. Also the patient who is in failure and cannot be controlled with medical measures should be considered for surgery, since some of the patients, even though the risk in surgery is high, could be salvaged.

American Journal of Medicine, New York

Abstracted by Hugo Dunlap Smith, M.D.

25, No. 6 (Dec.) 1958

A Controlled Study of Beta Hemolytic Streptococcal Infection in Rheumatic Families: I. Streptococcal Disease Among Healthy Siblings. Joseph M. Miller, Samuel L. Stancer, and Benedict F. Massell.—p. 825.

A Controlled Study of Beta Hemolytic Streptococcal Infection in Rheumatic Families: II. Penicillin Prophylaxis Among Rheumatic Fever Subjects, Comparing Different Regimens. Joseph M. Miller, Samuel L. Stancer, and Benedict F. Massell.—p. 845.

* An Appraisal of Fulminant Meningococcemia with Reference to the Shwartzman Phenomenon. William Margaretten and A. James McAdams.—p. 868.

Pseudomonas Septicemia: Observations on Twenty-Three Cases. Claude E. Forkner Jr., Emil Frei III, John H. Edgcomb, and John P. Utz.—p. 877.

Dominance and Recessivity in Medical Genetics.—A. C. Allison and B. S. Blumberg.—p. 933.

26, No. 1 (Jan.) 1959

Some Notes on the Composition and Metabolism of Connective Tissue. H. G. B. Slack.—p. 113.

Chronic Histoplasmosis: Report of a Patient Successfully Treated with Amphotericin B. Robert M. Greendyke and Nolan L. Kaltreider.—p. 135.

* Idiopathic Insulin-Resistant Diabetes Mellitus: Report of a Case Associated with Insulin Allergy. Ernest O. Friedlander and M. David Bryant Jr.—p. 139.

Radiation Nephritis: Report of a Fatal Case. Bernard F. Schreiner and Robert M. Greendyke.—p. 146.

A Case of Diffuse Histiocytosis X with Aplastic Anemia. H. James Day, Fred G. Conrad, and Charles A. Doan.—p. 152.

26, No. 2 (Feb.) 1959

* A Six-Month Evaluation of an Anabolic Drug, Norethandrolone, in Underweight Persons: I. Weight Gain. Robert N. Watson, Matthew H. Bradley, Robert Callahan, Bruno J. Peters, and Ross C. Kory.—p. 238.

* A Six-Month Evaluation of an Anabolic Drug, Norethandrolone, in Underweight Persons: II. Bromsulphalein (BSP) Retention and Liver Function. Ross C. Kory, Matthew H. Bradley, Robert N. Watson, Robert Callahan, and Bruno J. Peters.—p. 243.

Cholestasis Produced by the Administration of Norethandrolone. Fenton Schaffner, Hans Popper, and Eugene Chesrow.—p. 249.

Blood Glucose and the Liver. George F. Cahill Jr., James Ashmore, Albert E. Renold, and A. Baird Hastings.—p. 264.

Genetic Factors in Diseases of Connective Tissue: A Survey of the Present State of Knowledge. V. A. McKusick.—p. 283.

26, No. 3 (March) 1959

Sarcoidosis: An Analysis of Forty-Five Cases in a Large Military Hospital. Ellis P. Singer, Nestor M. Hensler, and Paul F. Flynn.—p. 364.

Mechanics of Respiration in Bronchial Asthma. Roe E. Wells Jr.—p. 384.

* Kuru: Clinical, Pathological and Epidemiological Study of an Acute Progressive Degenerative Disease of the Central Nervous System Among Natives of the Eastern Highlands of New Guinea. D. C. Gajdusek and V. Zigas.—p. 442.

Endocrine Control of Connective Tissue. Gustav Asboe-Hansen.—p. 470.

An Appraisal of Fulminant Meningococcemia with Reference to the Shwartzman Phenomenon.—Although the purpuric manifestations of meningococcemia have been attributed to the Shwartzman reaction, such a mechanism has been denied as the explanation for the bilateral adrenal hemorrhage seen in the Waterhouse-Friedrichsen syndrome, since such cases have lacked evidence of renal cortical necrosis, the finding considered characteristic of the generalized Shwartzman phenomenon. Margaretten and McAdams, however, not only noted venular and sinusoidal thromboses without vasculitis in the skin and adrenals suggest-

ing the localized Shwartzman reaction, but in 3 of 40 autopsied cases of meningococcemia also observed renal cortical necrosis. Because of these pathologic findings and because it is known that adrenal cortical steroid therapy (which was given to each of these three patients prior to the onset of shock) is an efficient method of potentiating the Shwartzman phenomena, the authors analyzed the mortality in 166 cases of meningococcemia not in shock at the time of admission to hospital. Of the 43 patients who received steroid therapy, 21% died while only 7% succumbed of the 123 not given steroids. (The clinical records of the latter group contain no information to suggest the patients were less severely ill than those who received steroids.) Since this difference in mortality was significant at a probability of $p = < 0.02$, the authors question the wisdom of adrenal steroid therapy in fulminant septicemia.

Idiopathic Insulin-Resistant Diabetes Mellitus: Report of a Case Associated with Insulin Allergy.—Insulin-resistant diabetes is defined as diabetes requiring 200 or more units of insulin daily for more than 48 hours in the absence of acidosis and infection. In reporting on a patient who needed as much as 6,000 units of crystalline insulin daily, Friedlander and Bryant review the factors responsible for insulin allergy and insulin resistance. Insulin resistance and insulin allergy need not occur simultaneously, although both are true immunologic phenomena. Insulin allergy, caused by a β-globulin, is manifested by skin sensitivity, generalized urticaria, and other allergic manifestations. A γ_2-globulin, which binds insulin, develops in all diabetics treated with insulin, but in the nonresistant subject rarely binds more than 10 units of insulin per liter of plasma, whereas in the resistant subject 80 to 400 units of insulin per liter may be bound, resulting in considerable interference with the biological activity of the injected insulin. Therapeutic measures for insulin resistance include the following: (1) saturation of the insulin-binding factors by large, preferably intravenously given, insulin doses (the slow release of the insulin from the binding antibody may allow a single morning injection of regular insulin to serve as a long-acting insulin); (2) avoidance of further stimulation of insulin antibodies by the exclusive use of crystalline insulin (impurities and additives used to prolong the action of insulin are thought to initiate the formation of the antibodies); (3) interference with the formation of insulin antibodies through the use of nitrogen mustards or adrenal cortical steroid therapy, and (4) inhibition of the insulin-binding action of the antibody by means of tolbutamide.

A Six-Month Evaluation of an Anabolic Drug, Norethandrolone, in Underweight Persons: I. Weight Gain.

A Six-Month Evaluation of an Anabolic Drug, Norethandrolone, in Underweight Persons: II. Bromsulphalein (BSP) Retention and Liver Function.

Norethandrolone (Nilevar) has been shown in animal experiments to have an anabolic effect equivalent to that of testosterone but with only 1/16 the androgenic action. Using a double-blind approach, Watson and his colleagues studied the effect of norethandrolone in 54 adults who had been chronically underweight and observed an average weight gain of 5.5 lb. in three months' time when the patients were receiving 25 mg. of the drug daily. In contrast, during the three-month control periods when placebos were given the average weight gain was only 0.3 lb. When norethandrolone was given for six months, the mean total weight gain was 9 lb. Of 25 subjects observed for six months following the withdrawal of the drug, 76% either maintained their weight or continued to gain. Increasing the dose to 50 mg. daily did not increase the weight gain.

Two forms of toxicity were noted. Amenorrhea, menorrhagia, or acne occurred in 8 of 10 women, these effects being more frequent on the 50 mg. dose and clearing when the dose was reduced or the drug stopped. The second toxic effect was evidence of some hepatotoxicity manifested chiefly by impairment of BSP excretion, which occurred in 74% of those studied. Abnormal BSP retention became apparent as early as one week after the onset of therapy when the dose was 50 mg. daily. The retention occurred less rapidly and less frequently when the dose was 25 mg. daily. Although none of the subjects manifested clinical evidence of liver dysfunction, SGOT was frequently mildly elevated, and in two patients there was transient slight elevation in the serum bilirubins and serum alkaline phosphatase. All of these changes reverted to normal after the cessation of therapy except in the case of one man who had a long history of alcoholism. Liver biopsies were done on seven patients and in four showed minimal abnormalities consisting of increased nuclear activity, slight to moderate lymphocytic infiltration, and in one patient minimal focal necrosis and bile stasis.

Kuru: Clinical, Pathological and Epidemiological Study of an Acute Progressive Degenerative Disease of the Central Nervous System Among Natives of the Eastern Highlands of New Guinea.—Among the natives of the Fore linguinal and cultural group in New Guinea, there exists an unusual, progressive neurological disorder which has been carefully studied by Gajdusek and Zigas. Approximately three-quarters of the cases occur in those over 20 years of age, and in this age group females account for 95% of the cases, whereas among children there is only a slight preponderance among girls. The illness has occurred in neighboring peoples only when there has been intermarriage with the Fore group. Also the illness has been seen distant from the Fore region only when members of the Fore group have moved into these new home sites, but it has not occurred among those who have occupied these distant homes either before or after the Fores. This evidence plus extensive evaluation of the native diet and of body chemistries tends to exclude a possible toxic etiology, while historical and clinical findings are against a postinfectious etiology. In contrast the epidemiology suggests that the disease is heredofamilial.

The clinical picture starts with locomotor ataxia, and soon there also is a distinctive intentional tremor of the trunk, extremities, and head. As these symptoms increase in severity, choreiform and athetoid movements may appear, and later there is incontinence, convergent strabismus, dysarthria, and emotional lability. The illness runs a relentless course, unaffected by numerous therapeutic efforts, and generally is fatal in six to nine months, accounting for as many as 50% of the deaths in some of the tribal areas. Pathologic examination has revealed widespread neuronal and myelin degeneration and astroglial and microglial proliferation involving primarily the cerebellum and extrapyramidal system, but also to some degree the anterior horn cells, inferior olive, thalamus, and pontine nuclei.

American Review of Tuberculosis and Pulmonary Diseases, New York

Abstracted by Edwin L. Kendig Jr., M.D.

79, No. 5 (May) 1959

* Segmental Atelectasis in Children with Primary Tuberculosis. Simon Frostad.—p. 597.

Serologic Relationship of Old Tuberculin-Sensitized Sheep Erythrocytes and Trypsinized Human Erythrocytes. Edwin V. Buehler and Melvin S. Rheins.—p. 622.

Antigenicity of Antimycobacterial Serums. Melvin S. Rheins and Edwin V. Buehler.—p. 631.

Distinguishing Mycobacteria by the Niacin Test: A Modified Procedure. E. H. Runyon, M. J. Selin, and H. William Harris.—p. 663.

The Effect of Topical Hydrocortisone Acetate Ointment at the Site of Intracutaneous Tuberculin Reaction. D. Levy and W. F. Russell Jr.—p. 666.

Catalase and Peroxidase Activities of Isoniazid-Susceptible and Resistant Strains of M. Tuberculosis. F. P. Dunbar, E. McAlister, and M. B. Jefferies.—p. 669.

Urine Test for the Detection of PAS in Ambulatory Tuberculous Patients. M. J. Breite.—p. 672.

Effects of Kanamycin, Streptovaricin, Paromomycin, Novobiocin, and Ristocetin on Murine Leprosy. Y. T. Chang.—p. 673.

Elimination of Precleaning Cage-Laid Hens' Eggs in Preparation of Egg Fluid for Tuberculosis Bacteriologic Media. S. M. Townsend.—p. 677.

BCG Vaccination in Sweden: W. R. Barclay. Official Report of Committee of Swedish Association of Chest Specialists and Swedish Medical Board Surgical Reporting. D. V. Pecora. Rehabilitation and Occupational Therapy in Tuberculosis Hospitals. A. R. Allen. Sophistry in the Use of the Word "Minimal." J. B. Seaman.—p. 678.

79, No. 6 (June) 1959

The Correlation of the Reaction to Protein from Certain Mycobacteria (Paratubercle Bacilli) with the Reaction to Tuberculin (OT). Joseph D. Aronson and William Kraus.—p. 731.

Studies on the Virulence of Tubercle Bacilli Using P^{32}-Labeled Bacilli: I. The Comparison of Elimination in Vivo of P^{32} Derived from Heat-Killed Virulent and Avirulent Tubercle Bacilli. Yoshihire Yamamura, Junkichi Tani, Takeo Terai, and Yuichi Yamamura.—p. 738.

* The Incidence of Segmental Lesions in Primary Tuberculosis in Childhood, with Special Reference to the Effect of Chemotherapy. Gerard Lorriman and Francis J. Bentley.—p. 756.

Toxic Psychosis Due to Isoniazid: Report of Three Cases with Studies of Patterns of Isoniazid Inactivation in the Serum. Avrum B. Organick.—p. 799.

Differentiation of Human Tubercle Bacilli from Atypical Acid-Fast Bacilli: III. Modification of the Niacin Test, Using Tween-Albumin Liquid Medium. K. Konno and A. J. Sharra.—p. 810.

The Effects of Mechanical Agitation on the Growth of the H37Ra Strain of M. Tuberculosis. D. W. Weiss.—p. 813.

A New Method of Counting the Viable Organisms in BCG Vaccine. B. B. Diena, L. Eidus, and L. Greenberg.—p. 816.

Segmental Atelectasis in Children with Primary Tuberculosis.—The author reports a series of 90 children with segmental atelectasis following primary tuberculosis. Bronchial stenosis relating to lymph node impression was present in 67.8% and lymph node perforation of the bronchial tree in 27.8%. In only one child were the findings completely negative at bronchoscopic examination. Both the atelectasis (111 to 63) and the lymph node perforations (21 to 7) were more frequently found on the right side.

Eleven lymph node perforations appeared in the first half year after primary infection, with a slight increase four to six months after primary infection. There were nine cases in the second half of the year and one perforation was noted 33 months after primary infection.

Lymph node perforation was seen more frequently in the age group under 6 years of age (17 cases) and more frequently in boys than in girls. Lymph node perforations in children very often appeared without symptoms, but coincident with these perforations a simultaneous clearing of the atelectatic zones was observed in the lungs of the children. The perforations appeared in spite of antituberculous chemotherapy, and even 12 to 14 months of chemotherapy did not prevent a lymph node perforation.

Abnormal bronchograms were noted in 27 of 33 children.

Intimate infectious contact with a tuberculous mother did not appear to have a more serious course than contacts with other sources of infection.

The Incidence of Segmental Lesions in Primary Tuberculosis in Childhood, with Special Reference to the Effect of Chemotherapy.—Plettenberg has suggested that treatment of primary pulmonary tuberculosis with isoniazid tends to precipitate rupture of enlarged hilar lymph nodes into the bronchi, and that in treated cases lobar atelectasis takes longer to resolve than in those untreated. The authors undertook this work in order to study the problem further by comparing the incidence of segmental lesions which developed in children admitted to High Wood Hospital with the initial classification of simple primary pulmonary tuberculosis and treated with chemotherapy with those which occurred in a similar group not so treated.

The study includes 107 consecutive cases of primary pulmonary tuberculosis in children under 5 years of age. Of these, 26 (24%) developed segmental lesions. Considering only those children who received isoniazid and another drug, 7 of 16 less than 2 years old (44%) developed segmental lesions compared with 2 of 10 (20%) given no chemotherapy.

For children between 2 and 5 years of age, the corresponding figures were 2 segmental lesions in 16 treated patients (12.5%) and 8 segmental lesions in 40 untreated patients (20%). The authors note that these numbers are too small to be statistically significant. Further, they point out that, even if chemotherapy produces a higher proportion of segmental lesions in children less than 2 years of age, such a disadvantage is outweighed by the advantage of preventing hematogenous disease.

Canadian Medical Association Journal, Montreal

Abstracted by H. M. Keith, M.D.

80, No. 8 (April 15) 1959

* Congenital Toxoplasmosis in Twins. B. Benjamin, Helen F. Brickman, and A. Neaga.—p. 639.

80, No. 9 (May 1) 1959

Congestive Heart Failure Caused by Sensitivity to Diphenylhydantoin (Dilantin Sodium). Sidney A. Carlen.—p. 725.

80, No. 10 (May 15) 1959

* An Analysis of the Causes of Perinatal Death. J. R. Mitchell, Georgina Hogg, A. J. DePape, E. J. N. Briggs, and H. Medovy.—p. 796.

* Factors Affecting the Prognosis for Survival in Prematurely Born Infants. K. G. Phillips, J. G. Armstrong, and B. G. Delta.—p. 800.

80, No. 11 (June 1) 1959

Sudden Unexpected Death in Infants. C. P. Handforth.—p. 872.

Toxoplasmosis. G. E. French.—p. 910.

80, No. 12 (June 15) 1959

* The Management of Idiopathic Thrombocytopenic Purpura. A. A. Cooperberg.—p. 937.

* Scurvy and Its Prevention by Vitamin C Fortified Evaporated Milk. D. Grewar.—p. 977.

Vaccination Against Poliomyelitis with Attenuated Live Virus. D. R. E. MacLeod.—p. 998.

81, No. 1 (July 1) 1959

* Poliomyelitis in Manitoba—1958. J. C. Wilt, R. M. Creighton, A. J. W. Alcock, W. Stackiw, and L. Nagel.—p. 1.

* Seasonal Aseptic Meningitis Caused by Coxsackie and ECHO Viruses, Toronto, 1957. Mairin Clarke, Margaret Hunter, G. A. McNaughton, D. von Seydlitz, and A. J. Rhodes.—p. 5.

81, No. 2 (July 15) 1959

* Hypertension in Children. R. J. Slater, D. W. Geiger, P. Azzopardi, and B. W. Webb.—p. 71.

Congenital Toxoplasmosis in Twins.—Six instances of toxoplasmosis in twins have been published, and the authors report the seventh. In one of the twins the signs and symptoms were very marked neonatally, and this infant died within one month. In the other they were so slight that diagnosis was made only in the fourth month by means of serological and minor ophthalmological findings.

Detailed pathological findings are reported in the one case. There was extensive diffuse meningoencephalitis, and hydrocephalus, ependymitis, right frontal lobe abscess, and brain calcification were present. There was also diffuse chorioretinitis with detachment of the retina of the right eye, as well as slight pericarditis, myocarditis, and interstitial pancreatitis.

The surviving twin had bilateral chorioretinitis but remained otherwise well up to the age of 14 months.

There is a discussion of the etiological factor and clinical manifestations of toxoplasmosis. Acquired Toxoplasma infection in the pregnant woman constitutes a serious threat to the fetus. The chief laboratory diagnostic aid is the dye test of Sabin and Feldman. The cutaneous test may be negative in active cases. Demonstration of parasites by animal inoculation supplies proof of the diagnosis.

Pyrimethamine and sulfonamides are therapeutically active against toxoplasma, but had no effect on the infant reported here.

There are three photographs, three photomicrographs, and one table.

An Analysis of the Causes of Perinatal Death.—A total of 707 neonatal deaths and stillbirths have been reviewed. The average perinatal mortality rate was 26.9.

Autopsies were performed on 94.5% of cases, and in 77.9% a pathologic diagnosis was made. However, autopsy did not reveal definite findings in 148 cases (22.1%). All the major pathologic findings are outlined in a table, and the remaining cases are discussed and grouped as to possible etiology. The major pathologic findings were anoxia, abnormal pulmonary ventilation, congenital malformations, infections, hemolytic disease, and trauma.

Factors Affecting the Prognosis for Survival in Prematurely Born Infants.—During 17 months, 329 liveborn premature infants were observed. There were 31 deaths in the first seven days. Each infant at birth was given an Apgar rating, and respiratory rates were measured at two-hourly intervals for 48 hours and at four-hourly intervals for the next three days. There was a high degree of correlation between the Apgar rating at birth, and the incidence of death within seven days, in infants over 1,750 gm. This was not true of infants under this weight.

Bradypnea which persisted beyond the first hour was a sinister sign. A rising respiratory rate during the first 24 hours of life was characteristic of most of the infants who died within seven days. However, this same pattern was observed among infants who survived, and whose birth weight was under 1,750 gm.

Sudden Unexpected Death in Infants.—The author describes the pathologic findings in 12 infants who died unexpectedly, all less than 6 months of age. All 12 had petechial hemorrhages in the lungs, heart, or thymus. No internal obstruction of the airway was noted in any infant, and no gross abnormalities found in the larynges. No constant bacterial flora was isolated from the heart, blood, or lungs.

The author then showed that it was possible to produce fatal respiratory arrest in rats by temporary (70 seconds) blocking of the airway. Autopsy examination of the rats showed intrathoracic petechial hemorrhages, pulmonary congestion and edema, resembling those found in the infants.

It is suggested that in the infants temporary obstruction by laryngospasm or bronchospasm (due to infection) may cause sudden death.

Hypertension in Children.—Most causes of elevated blood pressure are common to both children and adults, such as diseases of the renal, endocrine, and central nervous systems. Essential hypertension, however, is rare in children. The authors outline studies which may be carried out in the physician's office, and indicate further detailed studies to determine etiology. Renal dysfunction is the commonest cause of hypertension; others are cardiovascular disease, adrenal lesions, pheochromocytoma, neurological conditions, and poisoning, such as lead, etc.

Treatment is based upon correction of the underlying cause, and treatment of the hypertension per se, with reserpine (0.01 mg/lb.) and hydralazine (apresoline, 0.3 mg/lb.) in divided doses. Magnesium sulfate is also used in hypertensive crises.

Eight cases are reported in detail, illustrating the various clinical findings. There are three figures and three tables, the latter with footnotes as to normal values for the blood pressures, etc., in children.

The Management of Idiopathic Thrombocytopenic Purpura.—The author treated 23 consecutive patients (mainly adults) who had idiopathic thrombocytopenic purpura. Nine were treated without corticosteroids and fourteen were treated with cortisone, hydrocortisone, prednisone, and dexamethasone. Three patients died of cerebral hemorrhage before corticosteroids were available. There were no deaths in those treated with corticosteroids.

The author recommends that all patients with thrombocytic purpura should be treated with large doses (minimum of 40 mg. prednisone daily) of corticosteroids as soon as the diagnosis is made. Three patients in each group had splenectomy and preparation of the patients with steroids has made this a safe and elective procedure.

Scurvy and Its Prevention by Vitamin C Fortified Evaporated Milk.—Three cases of infantile scurvy were treated with partially skimmed evaporated milk, containing not less than 5 mg. of ascorbic acid per fluid ounce of evaporated milk. This was found effective in treating scurvy, and the author recommends fortifying evaporated milk with vitamin C as a means of preventing scurvy in infants.

Poliomyelitis in Manitoba—1958.—There were 152 cases of poliomyelitis studied in the reported outbreak. The highest incidence of the disease was in children from birth to 4 years of age, and it was severest in the 20- to 39-year age group. This has been interpreted to mean that the Salk vaccine was effective, since persons 6 to 19 years of age had higher rates of immunization. Only Type I poliovirus was isolated. Nine persons who received three doses of vaccine developed paralytic polio, whereas 77 unvaccinated persons developed paralytic disease, a ratio of 1:8.5. (The expected ratio would be 1:1 if the vaccine were ineffective.) There are five figures and seven tables, and the information given in them indicates the effectiveness of the vaccine in preventing paralytic poliomyelitis.

Seasonal Aseptic Meningitis Caused by Coxsackie and ECHO Viruses, Toronto, 1957.—Recently, two members of the enteric group of viruses; the Coxsackie and ECHO viruses, have come into prominence as the causal agents of seasonal outbreaks of aseptic meningitis.

Cases presenting without rash were indistinguishable clinically, although a variety of agents were found responsible for the illnesses. Distinctive were cases of rubelliform rash in association with the aseptic meningitis syndrome. ECHO Type 9 was the agent chiefly associated with cases of rash, although one such case yielded an unidentified ECHO virus.

From the total of 51 cases, 36 viruses were isolated by inoculation of human amnion or monkey kidney cells. Viruses were identified as belonging to the following established types: Coxsackie A9, B3, B5; ECHO types 6 and 9. Fifteen strains were unidentified but could be allocated provisionally to three groups: nine unidentified ECHO viruses, four Coxsackie A viruses, and two strains of mumps virus.

Serological evidence, combined with the results of tests on blood and cerebrospinal fluid, suggested that the stool isolates were active agents in the meningitis syndrome.

Thus, of the total 51 cases, 48% were due to ECHO viruses and 18% were due to Coxsackie viruses. An additional 14% of cases were established on serological grounds as due to mumps. The remaining 20% of cases, yielding no evidence of infection with enteric viruses or mumps, provide a problem for future years.

Journal of the American Medical Association, Chicago

Abstracted by Don M. Hosier, M.D.

169, No. 12 (March 21) 1959

* Simplified Screening Test for Cystic Fibrosis of the Pancreas. Edwin M. Knights Jr., James S. Brush, and John Schroeder.—p. 1279.

170, No. 5 (May 30) 1959

Intradermal Immunization Against Asian Influenza in Children. Robert C. Rendtorff, Lillie C. Walker, M. Eloise Rowland, and Henry Packer.—p. 524.
Experiences with General Anesthesia in Patients with Familial Dysautonomia. Marilyn M. Kretchman, Herman Schwartz, and Emanuel M. Papper.—p. 529.

Simplified Screening Test for Cystic Fibrosis of the Pancreas.—Measurement of the chloride excreted by sweat glands in the hand has become a well-established diagnostic screening procedure for cystic fibrosis of the pancreas. The agar plates first described by Shwachman and Gahm in 1956 and now generally used to detect an abnormal amount of chloride in hand sweat have, according to the authors, some inherent disadvantages: The plates are bulky and must be refrigerated during storage; children tend to dig their fingers into the agar during testing, and the method provides no permanent record of the reaction.

This procedure has been further modified and simplified by the impregnation of filter paper with silver chromate. The method of preparing the papers is described in detail.

The results of this test are similar to those obtained by the agar plate method but has the added advantages of being less expensive to prepare and much easier to store, and it provides a lasting record of the reaction.

Journal of Pediatrics, St. Louis

Abstracted by Demetrius G. Traggis, M.D.

54, No. 3 (March) 1959

Chronic Lead Poisoning. G. J. Cohen and W. E. Ahrens.—p. 271.
Hemangioma with Thrombocytopenia. H. W. Dargeon, A. C. Adiao, and G. T. Pack.—p. 285.
The Selenium Concentration in Placental Tissue and Fetal Cord Blood. D. M. Hadjimarkos, C. W. Bonhorst, and J. J. Mattice.—p. 296.
* A Disturbance of Carbohydrate Metabolism Caused by Lesions of the Central Nervous System.—R. D. B. Williams.—p. 299.
The Acquisition of Fecal Flora by Infants from Their Mothers During Birth. F. E. Gareau, D. C. Mackel, J. R. Boring, F. J. Payne, and F. L. Hammett.—p. 313.
The Parents of Retarded Children Speak for Themselves. C. H. Waskowitz.—p. 319.
The Vectorcardiogram of Malnourished Children During the First Month of Life. A. Castellanos, L. Azan, J. A. Junco, and N. Taquechel.—p. 330.
Is There a Rheumatic Constitution? E. F. Diamond.—p. 341.
Cardiovascular Surgery in a Children's Hospital: II. Cyanotic Lesions; A Review of 193 Operations. R. Ash, J. Johnson, C. E. Koop, S. Friedman, and W. Rashkind.—p. 348.
Galactosemia Presenting with Gangrene. P. J. Colipp and G. N. Donnell.—p. 363.
Duodenal Ulcer with Intestinal Obstruction in a Newborn Child. C. H. Floyd.—p. 369.
Cellulitis of the Leg Due to Type B Hemophilus Influenzae. O. G. Thilenius and R. E. Carter.—p. 372.
Hemoglobin S—Hereditary Spherocytosis. B. Jones and W. G. Klingberg.—p. 375.
The Children's Medical Center.—p. 379.
Glandular Toxoplasmosis. R. J. Blattner.—p. 388.
Obesity in Children. H. Bakwin.—p. 392.

A Disturbance of Carbohydrate Metabolism Caused by Lesions of the Central Nervous System.—The author reports the case of a 4-year-old boy who, previously well, awakened suddenly with vomiting and was found to be delirious, with gasping respirations and mottling of skin. Pupils small, neck stiff, temperature 104 F. Lumbar puncture showed bloody fluid. Urine 4+ sugar, but no acetone. Hydration good. Blood sugar 139 mg. %. At first treated with insulin but soon sugar began to drop (reached 24 mg. %), and glucose was given I. V. Second lumbar puncture also revealed bloody spinal fluid. Convulsions and other neurological signs developed. Patient died. At autopsy an extensive ependymoma was found invading the base of the brain from the pons anteriorly to surround the optic chiasma and the stalk of the pituitary. Both right and left thalami involved, more so on the right. A recent hemorrhage into the lateral ventricle was found. The case was reported because of the glycosuria and hyperglycemia which was present, making the diagnosis of diabetes a prominent one, al-

though hydration was good and acetonuria was absent. The author discusses the experimental work which has been done on animals in which injury to various areas of the brain, chiefly the hypothalamic area, has produced glycosuria, hyperglycemia, and sometimes hypoglycemia. He also reviewed fourteen cases in the literature in which lesions in the brain and glycosuria and hyperglycemia coexisted. Several had been considered as diabetic for as long as five years. In some the pancreas was normal. The diabetes tended to be mild, often without acetonuria and after responding poorly to insulin. The author calls attention to the possibility of brain pathology in patients presenting with hyperglycemia and glycosuria especially when other signs such as dehydration are minimal or absent.

Medizinische Klinik, Munich

Abstracted by Samuel Amberg, M.D.

54, No. 5 (Jan. 30) 1959

* The Causal Treatment of Strabismus. H. Görtz.—p. 174.

54, No. 6 (Feb. 6) 1959

* A New Combination Therapy of Obdurate Oxyuriasis. J. Hankiss.—p. 222.

54, No. 8 (Feb. 20) 1959

* Experience with a Tranquilizing and Hypnotic Remedy for Children, Free from Bromine and Barbituric Acid. J. Löw.—p. 317.

54, No. 10 (March 6) 1959

* The Perinatal Fatality of Infantile Eclampsia. H. Puder.—p. 406.

54, No. 12 (March 20) 1959

* The Effect of the Antihistaminic Systral on Blood Transfusions. W. Fliegel.—p. 523.

54, No. 17 (April 24) 1959

* Clinical Manifestations and Problems of Sporadic and Epidemic Infectious Mononucleosis.—p. 801.

54, No. 18 (May 1) 1959

* The Problem of Otoantritis of Infants in the Pathogenesis of Disorders of Nutrition. F. Thoenes.—p. 845.

54, No. 20 (May 15) 1959

* The Peculiarities of the Sleep of Children. Th. Hellbrügge.—p. 954.
* Motility in the Early Stages of Development of Children. The Hellbrügge and J. Lange.—p. 946.

The Causal Treatment of Strabismus.—The etiological factors of strabismus are presented and the therapeutic consequences are discussed.

A New Combination Therapy of Obdurate Oxyuriasis.—The report gives the results in adults who have proved resistant to usual treatment. Piperazine preparations or gentian violet are given orally. Hexylresorcinol 0.5 per milliliter was given as enema. Sometimes other substances were substituted for hexylresorcinol. The piperazines are given daily for eight days, the enemas in intervals of seven days from the 12th day. On the 32d day, the oral medication was resumed for another week and again after three months. Fourteen of eighteen patients treated were cured, repeated control examinations remaining negative. The others did not finish the treatment, or no control examinations could be made. The cellophane tests were repeated for months.

Experience with a Tranquilizing and Hypnotic Remedy for Children, Free from Bromine and Barbituric Acid.—Miramel is a commercial preparation containing extracts of valerian, melissa, and Asperula odorata (*Waldmeister*) and methylparafynol (Dormison) in a honey base. It was given to 526 children up to 8 years of age for insomnia, including pavor nocturnus or nervosity. The dosage was 1 teaspoon t.i.d. to the third year, 1 teaspoon g.i.d. to 8 years. For insomnia it was given for 8 to 10 days, for nervosity three to six weeks. The results are given as good in 85% in the 0-3-year group, 72% in the 3-5 year group and 81 per cent in the 5-8 year group. The preparation does not contain bromine or barbiturates. The scanty data support the expressed desirability of further study.

The Perinatal Fatality of Infantile Eclampsia.—On account of the dangers to the infant, cesarean section is advocated in cases of preeclampsia and eclampsia of the mother, which reduced the infant mortality in the author's material from 36.2% to 3.7%. However, in-

frequently the infant's liver may show lesions of typical eclamptic necrosis and one such case is described.

The Effect of the Antihistaminic Systral on Blood Transfusions.—Systral is (β-dimethylaminoethyl-ρ-chlor-α-methyl benzhydryl ether hydrochloride). Its action is antihistaminic and anticholinergic. It is administered in tablets or by intramuscular injection the evening before and on the day of the transfusion. Transfusion disorders were reduced from 3% to 1.86%.

Clinical Manifestations and Problems of Sporadic and Epidemic Infectious Mononucleosis.—The clinical manifestations and the changes in the blood picture as well as the value of the heterophile serum agglutination are discussed on the basis of 42 observations of sporadic and epidemic infectious mononucleosis mainly in adults.

The incubation could be determined rather accurately when a domestic servant entered the service of a family of which three members had the disease. It was five days. The heterophile serum agglutination (Hanganatziu-Deidner, Paul and Bunnel) is to be evaluated with caution in practice when it is not possible to obtain several control examinations.

The Problem of Otoantritis of Infants in the Pathogenesis of Disorders of Nutrition.—It is pointed out that in cases of nutritional disorders not responding to treatment with antibiotics and other measures an antrum mastoiditis has to be considered as the only or an important cause, particularly in the presence of a suspicious drum membrane. Experienced pediatrician and ear specialist together should decide whether surgery is indicated.

The Peculiarities of the Sleep of Children.—The total average duration of sleep of the young infant is given as 17 hours, that of the older infant as 12-15 hours. The infant's sleep is accompanied by a natural unrest. The requirement of the preschool child is on an average 12 to 13 hours, and the sleep is preponderantly limited to the night time. The school child requires 8 to 11 hours of sleep, depending on the age, and the tendency to sleep during the day becomes less and less. The adolescent still requires more sleep than the adult. Peculiarities mostly with regard to falling asleep are discussed and attention is to be given to these in order to avoid disturbances of sleep.

Motility in the Early Stages of Development of Children.—The motility of infants, including prenatal motility, is discussed in its relation to sleep, meals, and sensory perceptions, on the basis of the authors' own observations and the literature extending over a period of as long as about two years. During the first weeks of life the motility is preponderantly spontaneous under subcortical regulation; later, with progressing maturation of the cerebral cortex and the pyramidal tracts, regulated coordinated motions take their place. The motility during the first weeks of life is characterized by a change from several rest to activity cycles. At the end of the first year this polyphasic type of activity gives way to a monophasic type. Here the activity is more pronounced during the day, with longer rest periods at night.

Neue Oesterreichische Zeitschrift für Kinderheilkunde, Vienna

Abstracted by Hermann Vollmer, M.D.

5, No. 1, 1959

• Transferrin Deficiency in Children with the Nephrotic Syndrome. A. Rosenkranz and G. Weippl.—p. 1.
Constitutional Spherocytic Anemia in the Newborn. H. G. Wolf.—p. 9.
• Motor Patterns of Brain-Damaged Children. E. Frühmann.—p. 15.
• Sleep Position of Infants. L. Drexler and F. Wengraf.—p. 27.
Differential Diagnosis of Dystrophy in the First Year of Life. K. Kundratitz and O. Stur.—p. 39.
A Case of Chronic Erythroblastopenia. F. Ernst.—p. 47.
Nonspecific Spondylitis in Scheuermann's Disease. G. Felsenreich.—p. 52.

Transferrin Deficiency in Children with the Nephrotic Syndrome.—In 10 children with the nephrotic syndrome, a marked serum transferrin deficiency was found during the edematous and hypoproteinemic state. During remissions with normal serum protein, transferrin levels were normal.

Motor Patterns in Brain-Damaged Children.—In three brain-damaged children, a persistence of a coordinated mouth-arm movement was observed. This consists of a reflex opening of the mouth after stimuli to skin segments C5-D3.

Comment: The paucity of observations is hardly compensated by extensive interpretations and theories.

Sleep Position of Infants.—The typical sleep position of the upper extremities of young infants is revealed by roentgenographic studies as being due to a marked external rotation of the humerus. Specific anatomic characteristics of the newborn permit this position as a result of gravity after relaxation of the arm muscles.

Pédiatrie, Lyon, France

Abstracted by Jeana Levinthal, M.D.

13, No. 8, 1958

* Reflections on the Results Obtained in Our Premature Service. R. Sacrez and D. Willard.—p. 853.

Reflections on the Results Obtained in Our Premature Service.—The authors discuss the technique of care of prematures in Strasbourg during the periods 1927 to 1939, 1945 to 1951, and 1952 to 1956. In the first period, prematures were cared for in a general nursery with the full-term babies, and were not placed in incubators. Temperature was maintained at 37 C with hot water bottles, and feeding was started at 12 hours of age, with human milk. In the second period, the prematures were housed in a separate nursery, but there was crowding, and in spite of the use of penicillin and streptomycin, infections were numerous. Vitamin K was given, and feeding was started at 24 hours. In the third period, the service was divided into two nurseries, one with cubicles and incubators, and the other with cubicles. Antibiotics were given for at least 10 days to prematures born from difficult labor; feeding was started at 24 to 36 hours of age, and crowding was avoided. Retrolental fibroplasia appeared in 1952 with the use of incubators and oxygen therapy, and diminished when their use was restricted.

There has been a steady decline in the death rate of the babies weighing 1,500 gm. or more at birth, but very little change in the mortality of the smaller prematures, exactly as has been the experience in other centers. Many factors enter into the decreased mortality: longer hospital stay, improvement in the prevention and treatment of infection both by the creation of an aseptic service, and the prophylactic use of antibiotics in selected cases. The authors believe that the most important point has been the institution of an aseptic service, rather than the use of antibiotics.

Pediatriya, Moscow

Abstracted by Moses Grossman, M.D.

37, No. 7 (Jan.) 1959

Rational Use of Antibiotics in Pediatrics. Yu. F. Dombrovskaya.—p. 5.
Clinical and Laboratory Observations in ACTH and Cortisone Therapy of Rheumatic Fever. G. N. Speransky; R. L. Gamburg, and M. P. Matveev.—p. 16.
The Pathogenesis of "Infectious Heart" and Rheumatic Carditis. D. D. Lebedev; S. I. Petrov and I. M. Sopelkina.—p. 32.
* Pulmonary Segments and Pneumonias in Children. A. I. Strukov and I. M. Kodolova.—p. 53.
* Order to the Ministry of Health of the USSR, September 16, 1958, on the Dates for Childrens' Immunization.—p. 95.

37, No. 2 (Feb.) 1959

* Course of Scarlet Fever with Symptomatic Therapy Only. L. A. Antipova.—p. 12.
Changes in Content of Gamma Globulin and Other Protein Fractions in the Course of Scarlet Fever. In Tse-Jun.—p. 25.
Early Diagnosis and Treatment of Whooping Cough. I. Tanev, S. Zhelzkov, P. Scherov, M. Todorov, M. Boyadzhieva, and S. Avramov.—p. 33.
Treatment of Whooping Cough with Placental Gamma Globulin. K. S. Ladodo, and S. N. Babaeva.—p. 38.
* New Method of Treatment of Whooping Cough. S. G. Gimmelfarb.—p. 42.
Blood Changes in Acute Poliomyelitis. I. N. Sokolova and R. P. Khodorova.—p. 60.

37, No. 3 (March) 1959

Problems of Pediatrics in Early Childhood. G. N. Speransky.—p. 3.
Causes of Anorexia in Early Childhood and Its Therapeutic Management. T. S. Sokolova.—p. 16.
A Study of the Intestinal and Pancreatic Enzymes in the Duodenal Juice of Children. L. A. Diligenskaya and E. M. Valter.—p. 22.
A Study of Intestinal Enzymes in the Feces of Normal Children. L. S. Fomina.—p. 28.
* The Content of Vitamins B_1 and B_2 in Human Milk. R. B. Davidov and L. E. Gulko.—p. 32.
Pathologic Picture of Lungs and Viral Influenza in Early Childhood. L. O. Vishnevetskaya.—p. 58.
Bronchospasm as a Cause of Sudden Death of Young Infants. M. A. Samoteikin.—p. 62.

37, No. 4 (April) 1959

* Rheumatic Fever in Early Childhood. V. S. Andreeva.—p. 8.
Hormone Therapy of Juvenile Rheumatic Fever and Chronic Infectious Polyarthritis. I. I. Stepanova.—p. 22.
Capillary Permeability in Children with Rheumatic Fever. M. P. Dombrovskaya.—p. 31.
Streptokinase Skin Test in Children with Rheumatic Fever. Zh. Zh. Rapoport.—p. 42.
Interrelationship of Tuberculosis and Rheumatic Fever. I. A. Kresikova.—p. 49.
Prophylaxis of Dental Caries in Children. A. S. Rozental; E. O. Kotelnikova, and V. L. Zubkova.—p. 60.

Pulmonary Segments and Pneumonias in Children.—The authors have done extensive study of pulmonary segments of children of all ages, from the newborn through 15 years. Number of segments remains constant at all ages—10 segments on the right and 9 on the left. Whereas externally the segments of the small child are not exactly the same as those of an adult, there is considerable difference. Growth and differentiation of the pulmonary segments continues throughout childhood. There is greater differentiation of each segment from the other in small children than in adults.

The authors studied 40 children who died with the diagnosis of pneumonia. They found that in the upper lobes the most commonly involved segment is the second posterior one; in the lower lobes, primarily the 9th, 10th, and 7th segments are involved; in the left lung, additionally the 4th, 5th, and 7th segments. Of particular interest was the finding that the 6th segment was frequently the only one involved. Conversely, while the surrounding segments are involved, the sixth segment often remains free of disease. This underscores the anatomical isolation of the sixth segment. The authors emphasize that the segments in early childhood are particularly apt to have a triangular shape which can be seen on the AP and lateral x-ray projections. In conclusion, the authors stress the importance of understanding the pulmonary segments for better diagnosis and care of children with pneumonia.

Order to the Ministry of Health of the USSR, September 16, 1958, on the Dates for Childrens' Immunization.—It might be of interest to report on the present method of immunization in the children in the USSR as ordered by the Minister of Health:

Initial immunization:

BCG vaccination in the newborn nursery
Smallpox vaccination at 3 months
Vaccination for pertussis and diphtheria at 5 months
(three injections at 30 day intervals)
Poliomyelitis vaccination at 9 months
(two injections at 3- to 6-week intervals)

Revaccinations will be done as follows:

BCG at 2 years, 7 years, in the 4th grade, 7th grade, and 10th grade
Smallpox at 4 years, 8 years, 12 years, and 18 years;
Diptheria and pertussis at 14 months and at 3 years;
Diphtheria at 7 years and 12 years;
Poliomyelitis at 18 months.

Abstracter's Comment: This is the first change in routine immunization in USSR in five years and was occasioned by the introduction of poliomyelitis immunization. It is of interest to note that tetanus immunization does not appear to be routine.

The Course of Scarlet Fever with Symptomatic Therapy Only.—In the light of the mildness of scarlet fever during the past few years the authors decided to treat a series of patients without the use of penicillin. Between 1956 and 1957, 154 patients were thus treated. The children picked for this group generally had rather mild cases of scarlet fever. The control group consisted of 430 cases treated with oral penicillin. A number of differences were noted. For instance, the disappearance of rash before the fifth day occurred in 23% of the symptomatic therapy group and 82% of the control group. By the fifth day, streptococci disappeared from the throat in only 6% of the symptomatic therapy group and 38% of the control group. The complicated course of the disease was noted in 60% of the study group and 24% of the control group. Because of complications it became necessary to institute treatment in 41% of the study group at a later time, usually between the 7th and 8th day of illness. There was an increased incidence of cervical adenitis, otitis media. Interestingly enough, no nephritis was noted in either group. The occurrence of late complications was almost identical in both groups—6% of the study group and 4% of the penicillin control group. One of the authors

concluded that penicillin therapy is the principal cause of the fact that modern scarlet fever is mild.

Abstracter's Comment: Interestingly enough, the editor appended a note stating that this is not his feeling and that the swings in the communicable disease becoming milder in recent years are difficult to explain as solely due to antibiotics.

New Method of Treatment of Whooping Cough.—The author reports on the treatment of 210 children with whooping cough, beginning in April, 1956, with a method including aerosol administration of 1 cc. of solution daily containing 100,000 units of streptomycin and 5% procaine. The author noted a rapid decrease in cough and vomiting. This was apt to occur particularly if therapy was started very early in the course of the disease. The effect was less noticeable in the very small infant, and the author relates this to the difficulty of administering aerosol to this group. The author recommends this method as a highly effective addition to the conventional methods of therapy of whooping cough.

The Content of Vitamins B_1 and B_2 in Human Milk.—The authors review the available literature on the content of vitamins B_1 and B_2 in human milk. Their findings are that the average content of thiamine in human milk is 200μg. per kilogram of milk—the range being between 111μg. and 279μg. The average content of riboflavin is 300 gamma—with a range of 61 to 771 gamma. Simultaneously, the content of thiamine and riboflavin was determined in cow's milk. Cow's milk contains twice the amount of thiamine and three times the amount of riboflavin as human milk. The content of the B vitamins in cow's milk is stable throughout the year. There is a distinct relation between the content of thiamine and the content of fat in human milk. The more thiamine, the higher the fat content. The authors conclude that supplementary thiamine in maternal diet would increase the fat content of her milk.

Rheumatic Fever in Early Childhood.—Between 1950 and 1957, the author studied a group of children with acute rheumatic fever between the ages of 1 and 3 years, in the city of Svirglovsk. During this time 1,693 were hospitalized with rheumatic fever. Among them were 36 children between the ages of 1 and 3 (2.1%). If first attacks only are considered, there were 33 children between 1 and 3 years out of a total of 945, or 3.5%. Of the 36 children 9 had a fatal outcome and 5 had myocarditis; 23 of the 36 children were considered to have a severe form of the disease. The commonest manifestations were those of polyarthritis. There was not a single case of chorea.

Radiology, Syracuse, N.Y.

Abstracted by William E. Anspach, M.D.

72, No. 4 (April) 1959

* The Elusiveness of Neoplasia Following Roentgen Therapy for Thymic Enlargement in Childhood. Leonid S. Snegireff.—p. 508.
* Genetic Effects in Children and Grandchildren, of Women Treated for Infertility and Sterility by Roentgen Therapy. Ira I. Kaplan.—p. 518.
A Geneticist Looks at the Radiation Hazard. William J. Schull.—p. 522.

72, No. 5 (May) 1959

* The Bone Lesions of Childhood Leukemia: A Survey of 140 Cases. James K. V. Willson.—p. 672.
* Staphylococcal Pneumonia in Children and Adults. Harvey I. Meyers and George Jacobson.—p. 665.
* The Radiographic Evaluation of Pulmonary Vasculature in Children with Congenital Cardiovascular Disease. Dolores-Crystal Arnois, Frederic N. Silverman, and Malcolm E. Turner.—p. 689.

The Elusiveness of Neoplasia Following Roentgen Therapy for Thymic Enlargement in Childhood.—A preliminary report is given of 148 persons who received roentgen irradiation in childhood and infancy because of an enlarged thymus gland. The report covers 23 untreated patients with thymic enlargement, and a comparison group of 162 patients without detectable enlargement of the thymus. To date, no malignant neoplasms have been found, although 75 of the patients treated for an enlarged thymus have been followed for over 20 years. Two patients developed benign thyroid conditions, and three died of nonmalignant disease. Likewise there was no evidence of cancer in the 162 patients used as a control. There were six deaths, all from nonmalignant disease. This is in marked contrast to the previously reported high incidence of cancer of the thyroid and of leukemia following irradiation for thymic enlargement. Some of the contributing factors to observed differences include such

variables as age at the time of roentgen therapy and total dose. The author believes that systematic registration and complete follow-up of all patients exposed to therapeutic doses of ionizing radiation should be done for all conditions other than malignant disease.

Much of the elusiveness in the study of neoplasia following roentgen therapy for thymic enlargement in children is traceable to the variables which occur in the selection of patients, the composition of groups, the age at time of treatment, and the dose given in different studies.

Comment: A variable not mentioned specifically by the author but one that has been of great importance to the abstracter, is the technique used in making chest roentgenograms of infants and young children. Films made at a short distance with the patient supine, almost routine procedure 15 or 20 years ago, often gave an erroneous impression of thymic enlargement.

Genetic Effects in Children and Grandchildren, of Women Treated for Infertility and Sterility by Roentgen Therapy.—An analysis is made of the genetic changes observed in two successive generations of the offspring of 644 women who had received roentgen therapy for a tissue dose of approximately 65 r to the ovaries and 90 r to the pituitary, with a follow-up in over 50% of the cases of 5 to 32 years.

Of the 543 normal healthy living children of the 566 born to the 351 women, 260 are boys and 283 girls, including five sets of twins. Twenty children died at or after birth and three children are alive with abnormalities.

Abnormalities occurred in but three living children born after irradiation of the mothers. One of these had but one finger on one hand and one toe on one foot. Another had slight mental retardation, and the third was a baby girl having six fingers on one hand.

It has been said that irradiation of females tends to create a condition of sterility in their progeny. To date this has not been evident in the author's series. At present 35 children of these irradiated women are married and 31 of these already have had a total of 46 normal children, that is, grandchildren of the originally irradiated women. Only one case in the author's group has malignant disease. This patient died from leukemia approximately one year after treatment, and it is not known whether the patient already had leukemia at the time of irradiation.

There has been no cancer or leukemia of any type noted in any of the children or grandchildren of the irradiated women over the course of the past 33 years.

Despite the pronouncements of geneticists that "there is no safe dose of irradiation," no increase in genetic damage was found in the 644 patients. The incidence of genetic damage to the children and grandchildren of this group is less than that in the normal population. Some have stated that the series studied is too small to yield significant data, but to the author the results are more impressive than geneticists' calculations based on theory.

The Bone Lesions of Childhood Leukemia: A Survey of 140 Cases.—Long-bone roentgen examinations in 140 cases of childhood leukemia were reviewed. The commonest abnormal finding was a transverse radiolucent line at the metaphyses of the long bones. Osteolytic destructive lesions and periosteal reaction were also observed.

The bone lesions of leukemia were compared with the bone lesions observed in 30 unselected cases of neuroblastoma, which may resemble leukemia radiologically, and with those in 25 cases of rheumatoid arthritis and 20 cases of anemia, which may bear a clinical resemblance to leukemia.

The occurrence of the transverse radiolucent line at the metaphysis in diseases other than leukemia was investigated by a review of 740 consecutive long-bone examinations, comprising all such studies made during one calendar year in the pediatric division of the Department of Radiology of the Johns Hopkins Hospital. This lesion was observed in 28 patients below the age of 2 years and in 4 patients over that age. The conclusion is offered that the presence of a radiolucent metaphyseal line in a child over the age of 2 years may be of significance in the diagnosis of leukemia. It was not observed in neuroblastoma, rheumatoid arthritis, or the anemias. Below the age of 2 years this lesion may occur in association with many chronic diseases.

The advanced destructive lesions of leukemia present a characteristic pattern, unlike that in other diseases except metastatic neuroblastoma. Clinically the differential diagnosis from this latter condition is usually clear. Radiologically, the presence of a transverse radiolucent metaphyseal line associated with destructive lesions is in general indicative of leukemia, as this line is not observed in neuroblastoma.

When leukemia is suspected, yet unproved, roentgenograms of the long bones should be obtained.

Staphylococcal Pneumonia in Children and Adults.—Staphylococcal pneumonia has become an increasing problem in children, particularly in infants under 6 months of age, in whom the largest number of cases occur, and in whom the mortality rate is over 50%. The roentgenologic picture is usually characteristic enough to suggest an exact etiological diagnosis early in the course of the disease.

One of the most striking characteristics of the disease is the rapid change in the roentgen findings. The picture may change from one of minimal to very extensive involvement in a matter of hours. There is far from complete correlation between the roentgenologic appearance and the clinical condition of the patient. The pneumonic infiltration may be lobar or segmental in distribution; rarely is the infiltration bilateral.

Pleural effusion or empyema is an almost universal occurrence, and its presence in a young infant is nearly pathognomonic. Effusion or empyema may occur in pneumococcal or streptococcal pneumonia, but the authors have not seen it. Effusion may not be demonstrated on the initial examination but is usually present subsequently. Not infrequently, empyema is seen in the first chest roentgenogram. It may be so extensive as to obscure everything else in the involved hemithorax.

Pneumatocele formation is a regular feature in staphylococcal pneumonia and is quite diagnostic. Pneumatoceles tend to appear later in the course of the disease, but when they are seen early they give a very accurate indication of the nature of the illness. They are differentiated from lung abscesses by their thin walls and their tendency to rapid change in appearance, size, and location. Little correlation is noted between the presence and number of pneumatoceles and the clinical condition. Eventually they disappear completely. Pneumothorax is another characteristic finding, also pyopneumothorax. This is quite variable in extent, ranging from small, sometimes loculated areas, which may be hard to distinguish from pneumatoceles to massive tension pneumothorax. Only one case in the authors' group presented bilateral pneumothorax. This was in a 3-week-old infant, who survived.

The basic treatment of staphylococcal pneumonia depends on isolation of the organism by culture, and administration of the correct antibiotics. For the last few years almost none of the authors' cases has yielded organisms sensitive to penicillin, and almost all have been resistant to the tetracyclines. Most of the organisms in patients that were successfully treated were sensitive to chloramphenicol, erythromycin, or bacitracin. In addition to supportive measures, closed thoracotomy with insertion of an indwelling catheter into the pleural space, with constant suction, is frequently necessary and is often an immediate life-saving measure. The authors use streptokinase and streptodornase to irrigate the pleural space via the catheter. The course of the disease is frequently prolonged, often requiring two months of active treatment. Those infants and children that recover usually have no parenchymal findings after about three months.

The Radiographic Evaluation of Pulmonary Vasculature in Children with Congenital Cardiovascular Disease.—In a planned statistical study, a test was made of the ability of radiologists to recognize pulmonary under- and overvascularity by presenting the readers with films of 32 patients who were agreed by another group of readers to demonstrate pulmonary overvascularity, and films of 32 patients who were agreed to demonstrate pulmonary undervascularity. The radiologic assessment of the initial readers was supported by special studies, including cardiac catheterization, angiocardiography, operation, and in some instances necropsy. The 64 films thus available for analysis were matched by age, sex, and radiologic technique with normal chest films from the files of the Children's Hospital (Cincinnati). The resultant 128 chest films were randomized and presented three times to each of three "readers."

The first two readings were obtained with the chest obscured except for the lateral two-thirds of the right hemithorax. The third reading was made with the entire chest exposed as in a routine reading. Statistical analysis was made of the errors in classification in the two test groups of 32 films each. There was no appreciable difference between readers or readings, but there was a distinct difference in the number of errors related to the recognition of pulmonary undervascularity (Tetralogy of Fallot) in comparison with the recognition of pulmonary overvascularity. It is apparently much easier to recognize pulmonary overvascularity than it is pulmonary undervascularity in children with congenital malformations of the heart.

News and Comment

ANNOUNCEMENTS

Residencies in Pathology at Children's Hospital of Michigan.—Residencies in pediatric pathology are currently available at the Children's Hospital of Michigan. The pathology department is included in The Department of Laboratories, under the direction of Wolf W. Zuelzer, M.D., and is associated with an active hematology clinic and research laboratories. Clinical conferences and ward rounds are held regularly, and during the school year the hospital is the Pediatric Teaching Service of Wayne State University School of Medicine.

Positions are now available for one year, starting in July, 1960. Training is recognized by the American Boards of Pediatrics, Pathology, and Radiology and the Canadian Board of Pediatrics. The annual stipend is $2,400 and room and board.

All inquiries should be addressed to Jay Bernstein, M.D., Pathologist, Children's Hospital of Michigan, 5,224 St. Antoine St., Detroit 2.

Fellowships in Pediatric Endocrinology.—A number of fellowships are available for training in pediatric endocrinology at salaries of $5,000 to $5,500 per year. Such trainees must have completed residencies of two to four years on pediatric house staffs and, preferably, should be interested in academic or research careers. They will be accepted for periods of one or two years' training in pediatric endocrinology. One year will be spent largely in clinical diagnostic and investigative work and the other in laboratory research.

Those interested and qualified may write to Dr. Lawson Wilkins, The Harriet Lane Home, The Johns Hopkins Hospital, Baltimore 5, Md., sending *curriculum vitae* and letters of recommendation.

Books

BOOK REVIEWS

Practical Pediatrics. By R. Cannon Eley, M.D., Assistant Clinical Professor of Pediatrics, Harvard University, and Benjamin Kramer, M.D., Director of Pediatric Services, Maimonides Hospital, Brooklyn, and Clinical Professor of Pediatrics, Emeritus, State University of New York College of Medicine. Price, $7.00. Pp. 309, with eight photographic illustrations. McGraw-Hill Book Company, Inc., 330 W. 42d St. New York 36, 1958.

Eley and Kramer indicate their intention to describe in simple language accepted practice and procedures in pediatrics within the scope of the general practitioner in his everyday practice. They present their material in a simple conversational style which makes rapid and pleasant reading. Selection and limited space necessarily restrict discussion. The inclusion of an up-to-date bibliography would have helped overcome this partcular defect. Some duplication of material in various chapters is also somewhat detrimental to the over-all work.

The chapter on the newborn is well conceived but lacks helpful information on range of normal variations and values. The chapter on infant feeding is adequate but could have benefited by the inclusion of material covered in a later chapter on allergy regarding a feeding program for atopic infants. The authors retain the procedure for scarlet fever immunization after noting that "most physicians are of the opinion that immunization against this disease . . . is not indicated." It would seem that in a book with restricted space, procedures of doubtful value would have best been omitted. No mention is made of the availability of bovine antitetanus serum and rabies vaccine, or of desensitization to horse antitetanus serum.

This book is inadequate for the student of pediatrics but might provide a palatable superficial review of common pediatrics for a busy generalist.

J. V. Baublis, M.D.

Thrills and Regressions. By Michael Balint, M.D. Price, $4.00. Pp. 140. International Universities Press, Inc., 227 W. 13 Street, New York 11, 1959.

Michael Balint, a serious and yet popular writer in the field of psychoanalysis, has created a new book based on a commonly observed dichotomy—that of the difference between the individual who enjoys, participates in, and becomes a very real part of the exciting thrills of a carnival, and the other individual who shrinks, clings, and tries to avoid all the exciting rides. Dr. Balint has extended this common phenomenon into various approaches to life, trying to describe both the early background of those who become avid for the exciting, death-defying thrill, and those who tend to cling to the dependent security of the earth. He feels that this particular change occurs at a very early stage in personality development, when the individual becomes aware of the object outside himself on whom he is normally dependent. Some persons cling to this dependency; others go beyond it and defy it, but always eventually come back to earth.

The book is lightly and easily written, but is definitely a serious text and, in its latter chapters, becomes a technical book concerned chiefly with advice to psychoanalysts in the handling of the individuals who represent these two points on a wide continuum. It is to be recommended for those who have a good knowledge of basic psychoanalytic concepts and techniques. While its description of the approach people take to carnival activities has made the book popular enough to be reviewed in the lay journals, the actual body and style of the book make it very definitely into a textbook of psychoanalytic medicine.

Henry H. Work, M.D.

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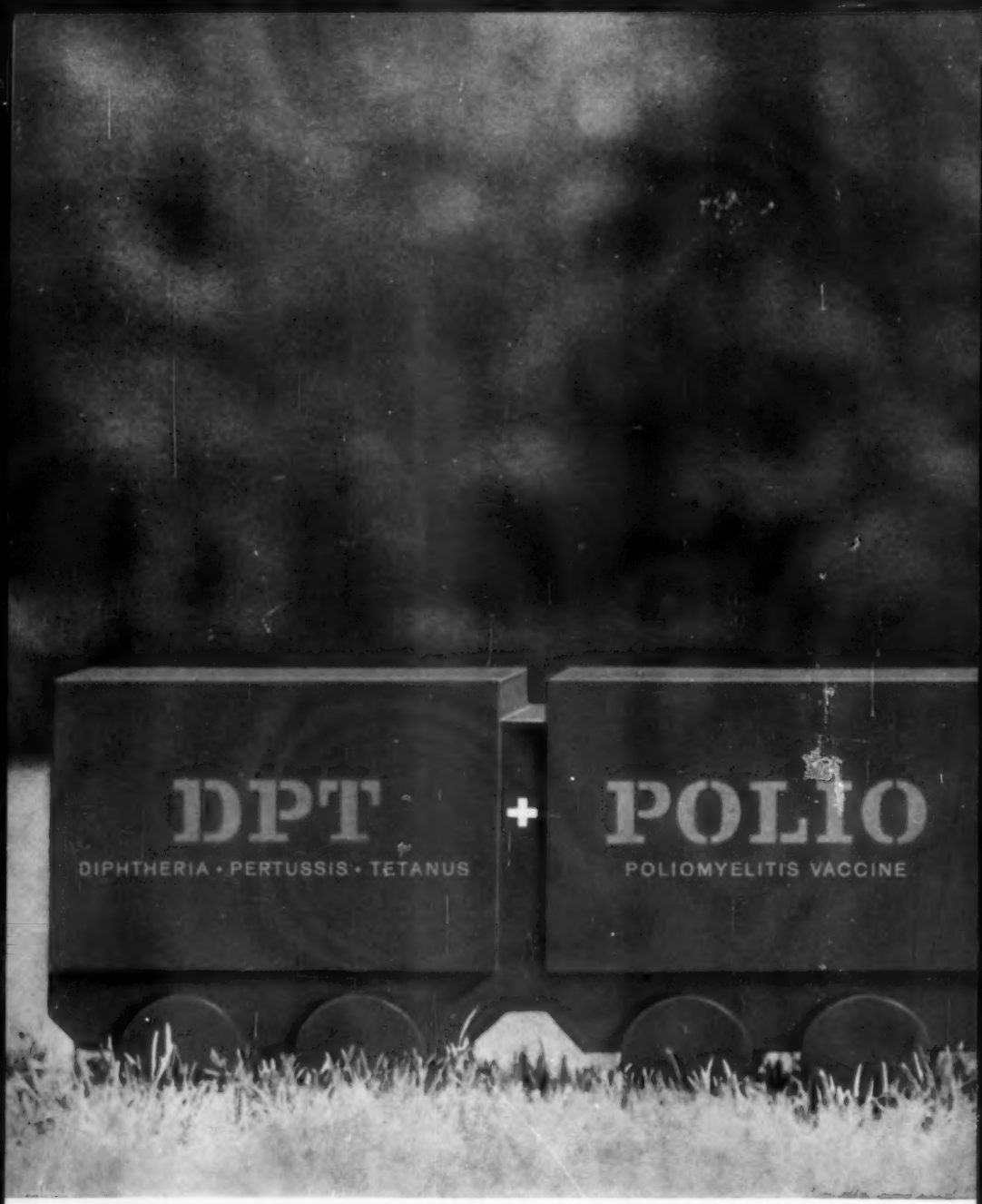

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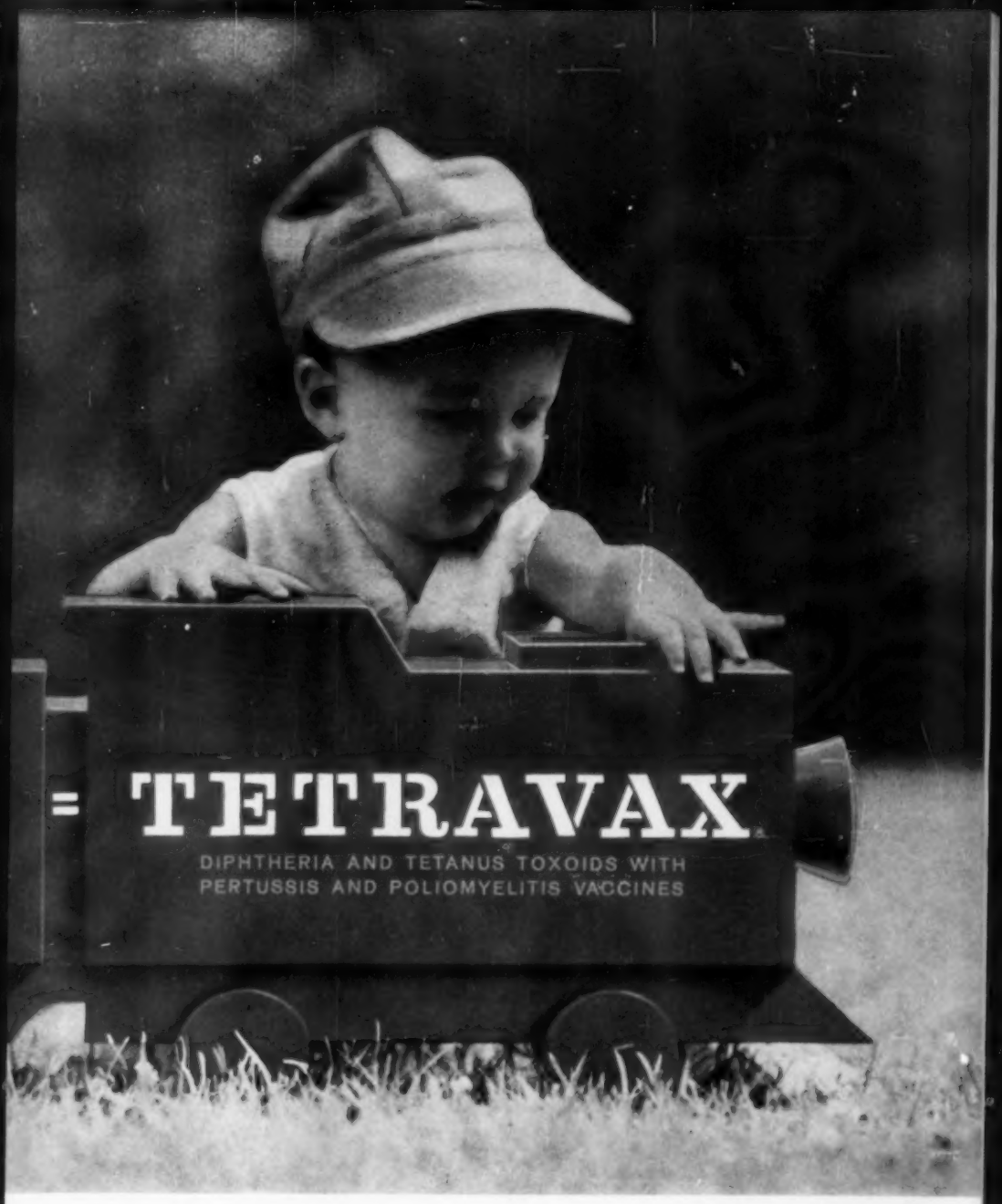

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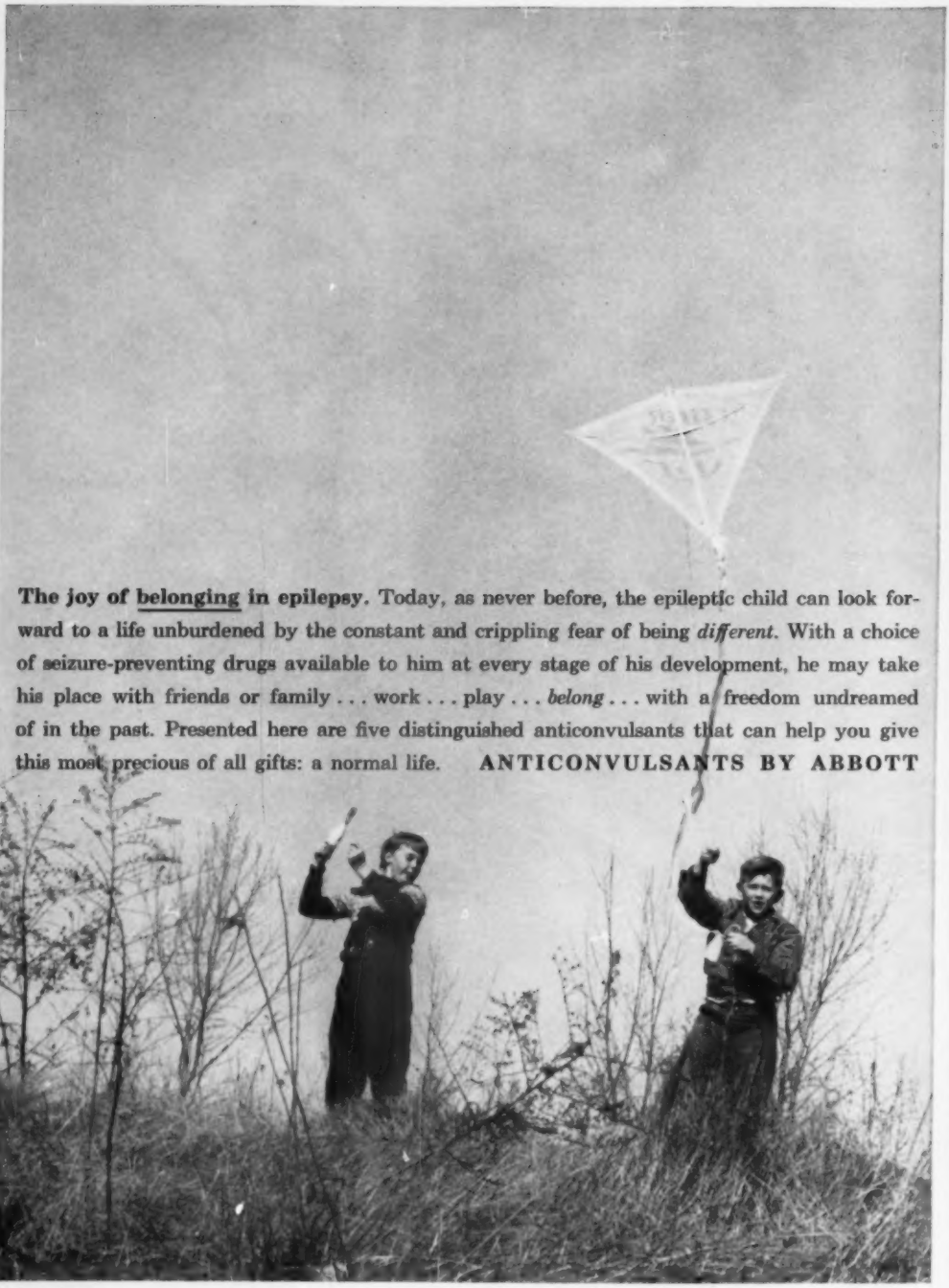

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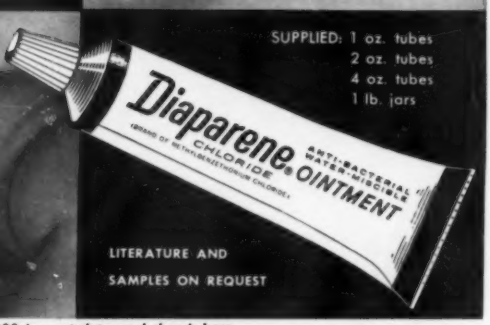

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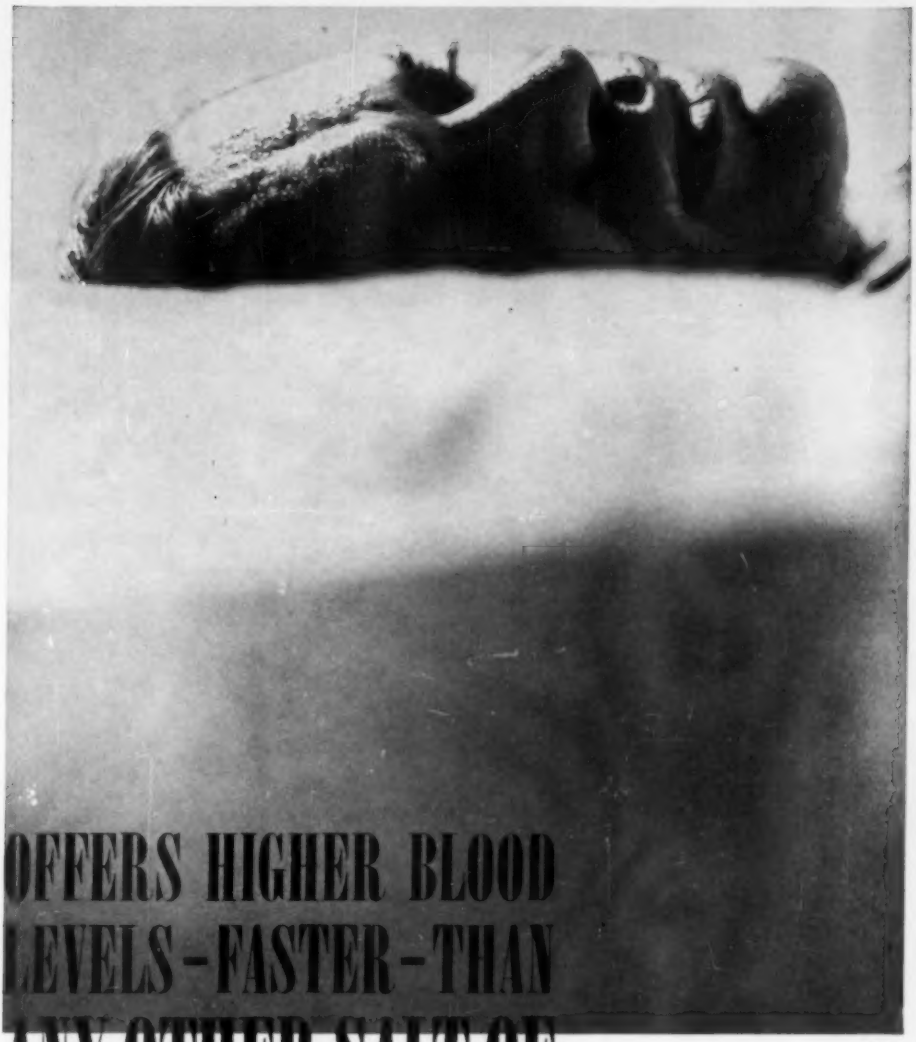

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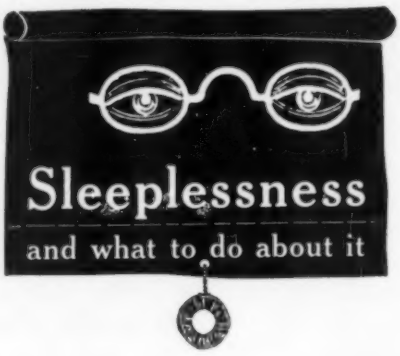

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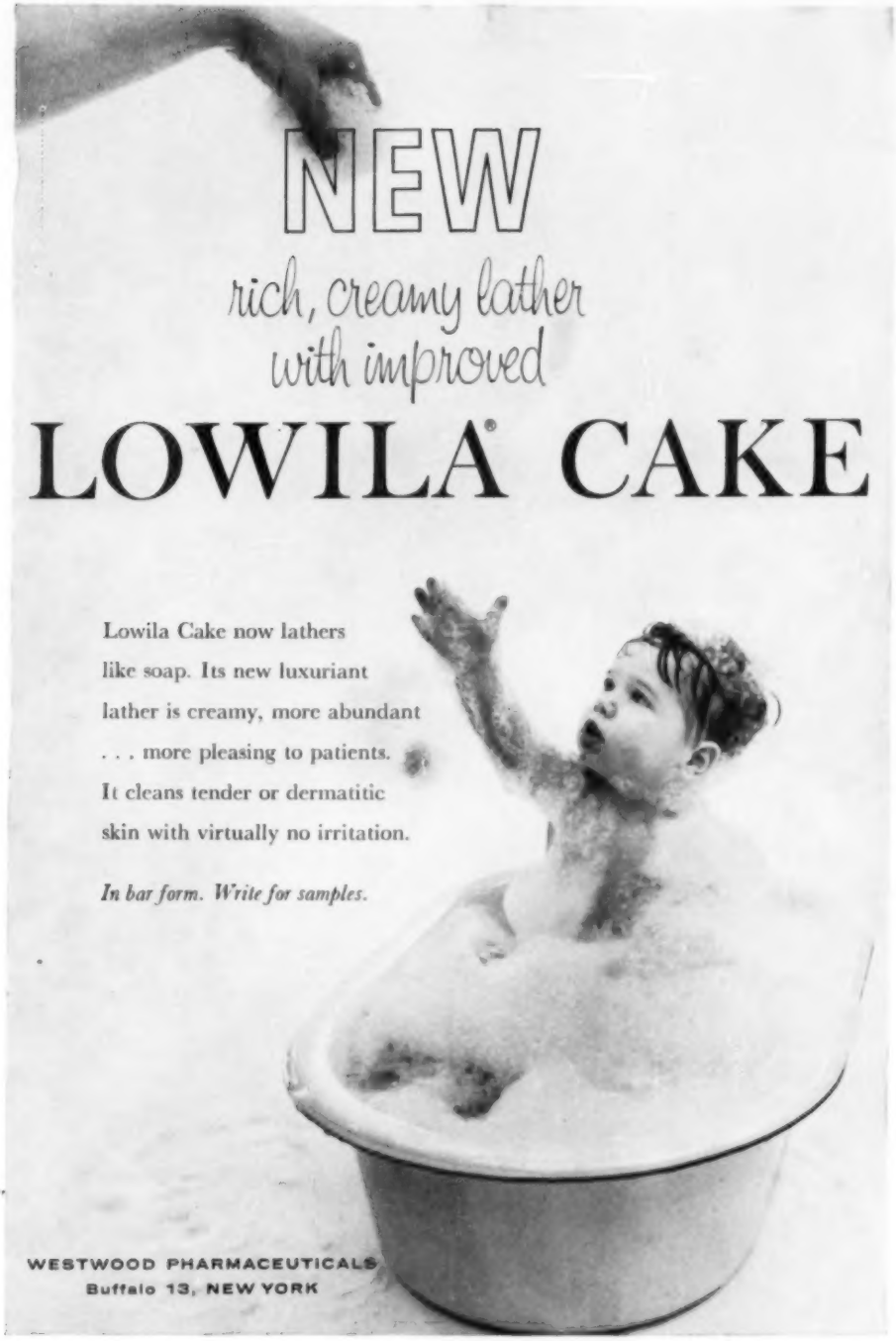
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1. Junkin, C. I.: *Canad. Anaesthetists' Soc. J.* 3:208, July, 1956.
2. Glaser, Jerome: *J. M. A. Georgia* 45:514, Dec., 1956.

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